PATENT SPECIFICATION

(11) 1 508 062

1 508 062

(19)

(21) Application No. 17557/75 (22) Filed 28 April 1975
(31) Convention Application No. 49/050 663
(32) Filed 9 May 1974
(31) Convention Application No. 49/052 254
(32) Filed 13 May 1974
(31) Convention Application No. 49/060 787
(32) Filed 31 May 1974
(31) Convention Application No. 49/050 663
(32) Filed 24 July 1974
(31) Convention Application No. 49/052 254
(32) Filed 7 Aug. 1974
(31) Convention Application No. 49/091 996
(32) Filed 13 Aug. 1974
(31) Convention Application No. 49/109 954
(32) Filed 26 Sept. 1974
(31) Convention Application No. 49/052 254
(32) Filed 12 Oct. 1974
(31) Convention Application No. 49/091 996
(32) Filed 28 Oct. 1974
(31) Convention Application No. 49/050/663
(32) Filed 6 Dec. 1974
(31) Convention Application No. 49/142 499
(32) Filed 13 Dec. 1974
(31) Convention Application No. 49/091 996
(32) Filed 17 Feb. 1975
(31) Convention Application No. 49/142 499
(32) Filed 26 March 1975
(31) Convention Application No. 50/037 207
(32) Filed 27 March 1975 in
(33) Japan (JP)
(44) Complete Specification published 19 April 1978
(51) INT CL² C07D 499/64; A61K 31/43, 31/545; C07D 501/20
(52) Index at acceptance

C2C 1175 1313 1314 1370 1371 1382 1384 1410 1432 1440 1450 1464 1474 1510 1530 1532 1562 1590 1600 1626 1651 200 211 213 214 215 220 221 225 226 22Y 246 247 250 251 252 253 254 255 256 25Y 280 282 28X 290 292 29X 29Y 305 30Y 313 316 31Y 324 334 338 339 33Y 342 34Y 351 352 355 35Y 360 361 364 365 366 367 368 36Y 373 375 37Y 386 387 390 396 401 40Y 43X 519 594 614 61X 625 628 62X 635 638 645 652 658 662 675 678 699 761 762 768 790 79Y KE KM RP TR TW

(72) Inventors ISAMU SAIKAWA, SHUNTARO TAKANO, CHOSAKU YOSHIDA, OKUTA TAKASHIMA, KAISHU MOMONOI, SEIETSU KURODA, MIWAKO KOMATSU, TAKASHI YASUDA and YUTAKA KODAMA

(54) NOVEL PENICILLINS AND CEPHALOSPORINS AND PROCESS FOR PRODUCING THE SAME

76

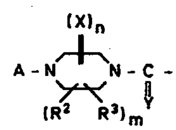
(71) We, TOYAMA CHEMICAL CO. LTD., a corporation organised under the laws of Japan, of 1—18, Kayabacho, Nihonbashi, Chuo-ku, Tokyo, Japan, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to novel penicillins and cephalosporins and to a process for producing the same.

The compounds of the present invention have various characteristics including a broad antibacterial spectrum against Gram-positive and Gram-negative bacteria, and effective antibacterial activity particularly against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus* species. Furthermore, the compounds of the present invention possess high resistance to β-lactamase produced from bacteria, and effective antibacterial activity even against clinical isolates of bacteria which are significant at present from the clinical standpoint. Accordingly, the compounds of the present invention are quite effective as therapeutic drugs for human and animal infectious diseases derived from the above-mentioned pathogenic microorganisms.

It has heretofore been known that 6-acylamino penicillanic acids and 7-acylaminocephalosporanic acids having an amino group at the α-position of the acyl group show strong antibacterial activity not only against Gram-positive bacteria but also against Gram-negative bacteria. However, there are the disadvantages that the known compounds described above show substantially no effective antibacterial activity against not only *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus* species, which have been known as causes for clinically serious infectious diseases but also resistant bacteria which are frequently isolated at present from many clinical hospitals. And they tend to be hydrolyzed with β-lactamase produced from many drug-resistant bacteria.

With an aim to obtain penicillins and cephalosporins having no disadvantages mentioned above, the present inventors conducted extensive studies to find that novel compounds of formula (I) which appears hereinafter, which are prepared by bonding the moiety,



wherein A, X, Y, R^2, R^3, n and m are as mentioned hereinafter, to the amino group in the acyl group of penicillins and cephalosporins, can sufficiently satisfy the above-mentioned aim and have extremely valuable therapeutic effects.

It is an object of this invention to provide novel penicillins and cephalosporins containing a mono- or di-oxo- or thioxo-piperazino(thio)carbonylamino group in molecule.

It is another object of this invention to provide novel penicillins and cephalosporins having a broad antibacterial spectrum.

It is a further object of the invention to provide novel penicillins and cephalosporins having high resistance to β-lactamase produced from bacteria.

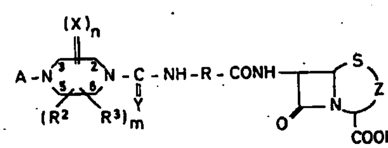
It is a still further object of the invention to provide novel penicillins and cephalosporins having effective antibacterial activity against clinical isolates of bacteria.

It is a still further object of the invention to provide a process for producing the novel penicillins and cephalosporins.

It is a still further object of the invention to provide a pharmaceutical composition containing the novel penicillins or cephalosporins as active ingredient.

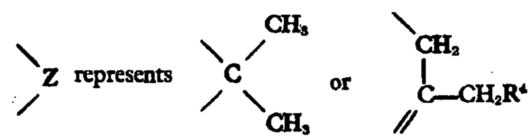
Other objects and advantages of this invention will become apparent from the following description.

The compounds of the present invention are penicillins and cephalosporins represented by the general formula (I),



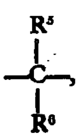
(I)

wherein R represents an amino acid residue; R^1 represents a hydrogen atom, an ester-forming group capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions, an ester-forming group capable of being easily removed by mamalium enzymic action, a silicon-, phosphorus- or tin-containing group which is capable of being easily removed by treatment with H_2O or an alcohol, or a conventional salt-forming cation, n represents 1 or 2; nX's, which may be the same or different, represent individually an oxygen or sulfur atom, and are linked in any combination at the 2-, 3- and 5- positions of the piperazine ring; m represents 4-n; each pair om R^2 and R^3 is linked to the same carbon atom, and m pairs of R^2 and R^3, which may be the same or different, represent individually a hydrogen atom, a halogen atom, a carboxyl group or an unsubstituted or substituted alkyl, cycloalkyl, aryl, acyl, aralkyl, alkoxycarbonylalkyl, acyloxyalkyl, alkoxy, alkoxycarbonyl, cycloalkyloxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, amino or carbamoyl group, any pair of R^2 and R^3 together with a comon carbon atom may form a cycloalkyl ring; A represents a hydrogen atom, a hydroxy group, a nitro group, a cyano group, or an unsubstituted or substituted alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloalkenyl, cycloalkadienyl, aryl, acyl, aralkyl, acyloxyalkyl, alkoxy, cycloalkyloxy, aryloxy, alkoxycarbonyl, cycloalkyloxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, carbamoyl, thiocarbamoyl, acylcarbamoyl, acylthiocarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkylsulfonylthiocarbamoyl, arylsulfonylthiocarbamoyl, sulfamoyl, alkoxycarbonylthioalkyl, alkoxythiocarbonylthioalkyl, amino or heterocyclic group; Y represents an oxygen or sulfur atom; and



where R^4 represents a hydrogen atom, a hydroxy group, a cyano group, an azido group, a quaternary ammonium group, or an unsubstituted or substituted alkoxy, aryloxy, aralkoxy, acyloxy, carbamoyloxy, guanidino, amino, alkylthio, arylthio, aralkylthio, acylthio, thiocarbamoylthio, alkoxythiocarbonylthio, aryloxythiocarbonylthio, cycloalkyloxythiocarbonylthio, amidinothio or heterocyclylthio group.

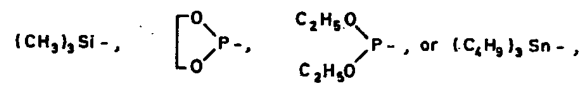
In the above-mentioned general formula (I) R represents an amino acid residue. Examples of such amino acid residue include residues of amino acids derived from various aliphatic, araliphatic, aromatic, alicyclic and heterocyclic compounds, which amino acids may have the amino group at a position such as α-, β- or γ-position to the carboxyl group. Preferable as said R is an α-amino acid residue represented by the formula



wherein R^5 is an alkyl group such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; a cycloalkyl group such as cyclopentyl, cyclohexyl, or cycloheptyl; a cycloalkenyl group such as cyclopentenyl, or cyclohexenyl; a cycloalkadienyl group such as cyclopentadienyl, or cyclohexadienyl; an aryl group such as phenyl or naphthyl; an aralkyl group such as benzyl or phenetyl; an aryloxy group such as phenoxy or naphthoxy; an alkylthioalkyl group such as methylthiomethyl, ethylthiomethyl, methylthioethyl or ethylthioethyl; or a heterocyclic group such as furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrazyl, pyrimidyl, pyridazyl, quinolyl, isoquinolyl, quinazolyl, indolyl, indazolyl, 1,3,4-oxadiazoyl, 1,2,4-oxadiazolyl, 1,3,4-thiadiazolyl or 1,2,4-thiadiazolyl; each group represented by said R^5 may be substituted by various groups, for example, halogen, hydroxy, nitro, alkyl, alkoxy, alkylthio, acyl, or alkylsulfonylamino; R^6 represents a hydrogen atom; and R^5 and R^6 together with a common carbon atom may form a cycloalkyl ring such as cyclohexyl or cycloheptyl; a cycloalkenyl ring such as cyclopentenyl or cyclohexenyl; or a cycloalkadienyl ring such as cyclopentadienyl or cyclohexadienyl.

In the general formula (I), R^1 is a hydrogen atom, a blocking group or a salt-forming cation. The blocking group may be any of those which have heretofore been

used in the field of penicillin or cephalosporin type compounds. Concretely, the blocking group includes (1) ester-forming groups capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions e.g. arylsulfonylalkyl groups such as toluene-sulfonylethyl, substituted or unsubstituted aralkyl groups such as benzyl, 4-nitrobenzyl, diphenylmethyl, trityl and 3,5-di(tert.-butyl)-4-hydroxybenzyl; substituted or unsubstituted alkyl groups such as tert.-butyl, trichloroethyl, phenacyl groups; alkoxyalkyl groups such as methoxymethyl; and unsubstituted or alkyl-substituted cyclic aminoalkyl groups such as piperidinoethyl, 4-methylpiperidinoethyl, morpholinoethyl or pyrrolidinoethyl, (2) ester-forming groups capable of being easily removed owing to enzymes in a living body, e.g. acyloxyalkyl groups such as pivaloyloxymethyl; phthalide group; and indanyl group; (3) silicon-containing groups, phosphorus-containing groups and tin-containing groups which are capable of being easily removed by treating with H_2O or an alcohol, such as



The examples of the blocking groups mentioned in above (1), (2) and (3) are merely typical, and other examples are disclosed in U.S. Patents 3,499,909; 3,573,296 and 3,641,018 and DOS 2,301,014; 2,253,287 and 2,337,105 and may be used in this invention. The salt-forming cation includes conventional cations which have heretofore been known in the field of penicillin or cephalosporin type compounds, ad preferable are those capable of forming non-toxic salts. The salts include alkali metal salts such as the sodium salt or the potassium salt; alkaline earth metal salts such as the calcium salt or the magnesium salt; ammonium salt; and salts with nitrogen-containing organic bases such as procaine, dibenzylamine, N-benzyl-β-phenethylamine, 1-ephenamine, or N,N-dibenzylethylenediamine. In addition to the above cations, there may be used cations capable of forming the salts with other nitrogen-containing organic bases, such as trimethylamine, triethylamine, tributylamine, pyridine, dimethylaniline, N-methylpiper-idine, N-methylmorpholine, diethylamine, or dicyclohexylamine. Furthermore, the cation includes quaternary ammonium groups formed at the 3-position of cephem ring, such as pyridinium, quinolinium, isoquinolinium and pyrimidinium. In this case, a betaine structure is formed in the molecule.

In the general formula (I), m pairs of R^2 and R^3, which may be the same or different, represent individually, a hydrogen atom; a halogen atom such as fluorine, chlorine or bromine; a carboxyl group; an alkyl group such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl; a cycloalkyl group such as cyclopentyl, cyclohexyl or cycloheptyl; an aryl group such as phenyl or naphthyl; an acyl group such as acetyl, propionyl, butyryl or benzoyl; an aralkyl group such as benzyl or phenethyl; an alkoxycarbonylalkyl group such as methoxycarbonylmethyl or ethoxycarbonylmethyl; an acyloxyalkyl group such as acetyloxymethyl, propionyloxymethyl, pivaloyloxymethyl or benzoyloxymethyl; an alkoxy group such as methoxy, ethoxy, propoxy or butoxy; an alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl; a cycloalkyloxycarbonyl group such as cyclopentyloxycarbonyl, cyclohexyloxycarbonyl or cycloheptyloxycarbonyl; an aralkoxycarbonyl group such as benzyloxycarbonyl or phenethoxycarbonyl; an aryloxycarbonyl group such as phenoxycarbonyl or naphthoxycarbonyl; an amino group such as amino, N-alkylamino (e.g. N-methylamino, N-ethylamino, N-propylamino or N-butylamino), N,N-dialkylamino (e.g. N,N-dimethylamino, N,N-diethylamino or N,N-dibutylamino), N-acylamino (e.g. N-acetylamino, N-propionylamino, N-butyrylamino or N-benzoylamino), and cyclic amino (e.g. pyrrolidino, piperidino, or morpholino); and a carbamoyl group such as carbamoyl, N-methylaminocarbonyl, N-ethylaminocarbonyl, N,N-dimethylaminocarbonyl or N,N-diethylaminocarbonyl. Further, R^2 and R^3 together with a common carbon atom may form a cycloalkyl ring such as a cyclopentyl, cyclohexyl or cycloheptyl group. Each of the groups mentioned above for said R^2 and R^3 may be substituted by various substituents, for example, halogen atoms, or alkyl, alkoxy, alkylthio, acyl or nitro groups.

In the general formula (I), A represents a hydrogen atom; a hydroxy group; a nitro group, a cyano group; an alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, or dodecyl; an alkenyl group such as vinyl, propenyl or butenyl; an alkynyl group such as propargyl; an alkadienyl group such as 1,3-butadienyl or 1,3-pentadienyl; a cycloalkyl group such as cyclopentyl, cyclohexyl or cycloheptyl; a cycloalkenyl group such as cyclopentenyl or cyclohexenyl; a cycloalkadienyl

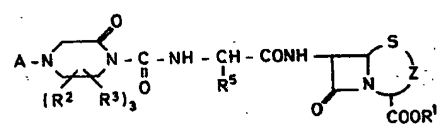
group such as cyclopentadienyl or cyclohexadienyl; an aryl group such as phenyl or naphthyl; an acyl group such as formyl, acetyl, propionyl, isovaleryl, caproyl, enanthoyl, capryloyl, palmitoyl, stearoyl, acryloyl, cyclohexanecarbonyl, benzoyl, phenylglycyl, furoyl or thenoyl; an aralkyl group such as benzyl or phenethyl; an acyloxyalkyl group such as acetyloxyethyl, pivaloyloxymethyl or benzoyloxymethyl; an alkoxy group such as methoxy, ethoxy, propoxy or butoxy; a cycloalkyloxy group such as cyclopentyloxy, cyclohexyloxy or cycloheptyloxy; an aryloxy group such as phenoxy or naphthoxy; an alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl or butoxycarbonyl; a cycloalkyloxycarbonyl group such as cyclopentyloxycarbonyl, cyclohexyloxycarbonyl, or cycloheptyloxycarbonyl; an aryloxycarbonyl group such as phenoxycarbonyl or (1- or 2-)naphthoxycarbonyl; an aralkoxycarbonyl group such as benzyloxycarbonyl or phenethoxycarbonyl; an alkylsulfonyl group such as methanesulfonyl, ethanesulfonyl, propanesulfonyl or butanesulfonyl; a cycloalkylsulfonyl group such as cyclopentanesulfonyl or cyclohexanesulfonyl; an arylsulfonyl group such as benzenesufonyl or (1- or 2-)naphthalenesulfonyl; a carbamoyl group such as carbamoyl, N-alkylaminocarbonyl (e.g. N-methylaminocarbonyl, N-ethylaminocarbonyl, N-propylaminocarbonyl or N-butylaminocarbonyl), N-arylaminocarbonyl (e.g. N-phenylaminocarbonyl), N,N-dialkylaminocarbonyl (e.g. N,N-dimethylaminocarbonyl or N,N-diethylaminocarbonyl), cyclic amino carbonyl (e.g. pyrrolidinocarbonyl, piperidinocarbonyl or morpholinocarbonyl); a thiocarbamoyl group such as thiocarbamoyl, N-alkylaminothiocarbonyl (e.g. N-methylaminothiocarbonyl, N-ethylaminothiocarbonyl or N-propylaminothiocarbonyl), N-arylaminothiocarbonyl (e.g. N-phenylaminothiocarbonyl), N,N-dialkylaminothiocarbonyl (e.g. N,N-dimethylaminothiocarbonyl or N,N-diethylaminothiocarbonyl), or cyclic aminothiocarbonyl (e.g. pyrrolidinothiocarbonyl, piperidinothiocarbonyl or morpholinothiocarbonyl); an acylcarbamoyl group such as N-acetylcarbamoyl, N-propionylcarbamoyl, N-butyrylcarbamoyl, N-benzoylcarbamoyl, N-furoylcaramoyl, or N-thenoylcarbamoyl; an acylthiocarbamoyl group such as N-acetylthiocarbamoyl, N-propionylthiocarbamoyl, N-butyrylthiocarbamoyl, N-benzoylthiocarbamoyl, N-naphthoylthiocarbamoyl, N-furoylthiocarbamoyl or N-thenoylthiocarbamoyl); an alkylsulfonylcarbamoyl group such as methanesulfonylaminocarbonyl, ethanesulfonylaminocarbonyl or butanesulfonylaminocarbonyl; an arylsulfonylcarbamoyl group such as benzenesulfonylaminocarbonyl or (1- or 2-)naphthalenesulfonylaminocarbonyl; an alkylsulfonylthiocarbamoyl group such as methanesulfonylaminothiocarbonyl, ethanesulfonylaminothiocarbonyl or butanesulfonylaminothiocarbonyl; an arylsulfonylthiocarbamoyl group such as benzenesulfonylaminothiocarbonyl or naphthalenesulfonylaminothiocarbonyl; a sulfamoyl group such as sulfamoyl, N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-butylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibtuylsulfamoyl, N-phenylsulfamoyl, N-benzylsulfamoyl, N-cyclopentylsulfamoyl or N-cyclohexylsulfamoyl; an alkoxycarbonylthioalkyl group such as methoxycarbonylthiomethyl, ethoxycarbonylthiomethyl, propoxycarbonylthiomethyl, butoxycarbonylthiomethyl or methoxycarbonylthioethyl; an alkoxythiocarbonylthioalkyl group such as methoxythiocarbonylthiomethyl, ethoxythiocarbonylthiomethyl, propoxythiocarbonylthiomethyl, butoxythiocarbonylthiomethyl or methoxythiocarbonylthioethyl; an amino group such as amino, N-alkylamino (e.g. N-methylamino, N-ethylamino, N-propylamino or N-butylamino), N,N-dialkylamino (e.g. N,N-dimethylamino, N,N-diethylamino or N,N-dibutylamino), N-acylamino (e.g. N-acetylamino, N-propionylamino, N-butyrylamino or N-benzoylamino), or cyclic amino (e.g. pyrrolidino, piperidino or morpholino); or a heterocyclic group such as thiazolyl, pyridyl, pyridazyl, pyrazyl, thiadiazolyl, triazolyl, tetrazolyl or quinolyl. Each of the groups mentioned above for A in formula (I) may be substituted by any of such substituents as, for example, halogen atoms, hydroxyl groups, alkyl groups, alkoxy groups, alkylthio groups, nitro groups, cyano groups, amino groups (e.g. dialkylamino or cyclic amino), carboxyl groups and acyl groups.

The quaternary ammonium groups for R^4 include pyridinium, quinolinium, isoquinolinium and pyrimidinium. Further, the organic group which is linked through O, N or S for R^4 includes alkoxy groups such as methoxy, ethoxy or propoxy; aryloxy groups such as phenoxy or naphthoxy; aralkoxy groups such as benzyloxy or phenethoxy; acyloxy groups such as acetyloxy, propionyloxy, butyryloxy, benzoyloxy, naphthoyloxy, cyclopentanecarbonyloxy, cyclohexanecarbonyloxy, furoyloxy or thenoyloxy; carbamoyloxy groups such as carbamoyloxy, N-methylaminocarbonyloxy, N,N-dimethylaminocarbonyloxy, N-acetylaminocarbonyloxy, phenylaminocarbonyloxy, benzylaminocarbonyloxy or cyclohexylaminocarbonyloxy; guanidino groups such as guanidino or N-methylguanidino; amino groups such as amino, N-alkylamino (e.g. N-methylamino, N-ethylamino, N-propylamino, N-butylamino, N-cyclohexylamino or N-phenylamino), N,N-dialkylamino (e.g. N,N-dimethylamino, N,N-diethylamino or

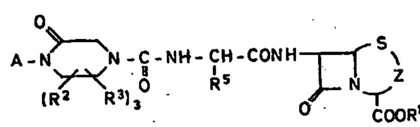
N,N-dibutylamino), and cyclic amino (e.g. pyrrolidino, piperidino or morpholino); alkylthio groups such as methylthio, ethylthio or propylthio; arylthio groups such as phenylthio or (1- or 2-)naphthylthio; aralkylthio groups such as benzylthio or phenethylthio; acylthio groups such as acetylthio, propionylthio, butyrylthio, benzoylthio, (1- or 2-)naphthoylthio, cyclopentanecarbonylthio, cyclohexanecarbonylthio, furoylthio, thenoylthio, isothiazolecarbonylthio, isoxazolecarbonylthio, thiadiazolecarbonylthio or triazolecarbonylthio; thiocarbamoylthio groups such as thiocarbamoylthio, N-methylthiocarbamoylthio, N,N-diethylthiocarbamoylthio, 1-piperidino-thiocarbonylthio, 1-morpholinothiocarbonylthio or 4-methyl-1-piperazinothiocarbonylthio; alkoxythiocarbonylthio groups such as methoxythiocarbonylthio, ethoxythiocarbonylthio, propoxythiocarbonylthio or butoxythiocarbonylthio; aryloxythiocarbonylthio groups such as phenoxythiocarbonylthio; cycloalkyloxythiocarbonylthio groups such as cyclohexyloxythiocarbonylthio; amidinothio groups such as amidinothio, N-methylamidinothio or N,N′-dimethylamidinothio; and heterocyclic thio groups such as oxazolylthio, thiazolylthio, isoxazolylthio, isothiazolylthio, imidazolylthio, pyrazolylthio, pyridylthio, pyrazinylthio, pyrimidinylthio, pyridazinylthio, quinolylthio, isoquinolylthio, quinazolylthio, indolylthio, indazolylthio, oxadiazolylthio, thiadiazolylthio, triazolylthio, tetrazolylthio, triazinylthio, benzimidazolylthio, benzoxazolylthio, benzothiazolylthio, triazolopyridylthio, purinylthio, pyridine-1-oxide-2-ylthio or pyridazine-1-oxide-6-ylthio. Each of the groups mentioned above for R^4 may be substituted by any of such substituents as, for example, halogen atoms, alkyl groups, alkoxy groups, alkylthio groups, nitro groups, cyano groups, acylamino groups, acyl groups, carboxyl groups or carbamoyl groups.

The above-mentioned compounds of formula (I) of the present invention have their optical isomers, and all of D-isomers, L-isomers and racemic compounds thereof are involved in the scope of the present invention.

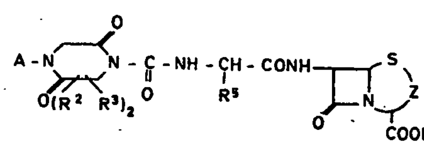
In the present invention, preferable compounds of the general formula (I) are as follows:



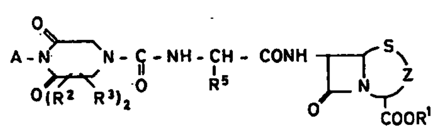
(Ia)



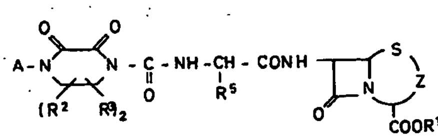
(Ib)



(Ic)

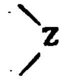


(Id)



(Ie)

wherein R^1, R^2, R^3, A, R^5 and

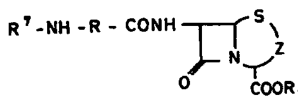


are as defined above.

The compounds of formula (I) of the present invention are produced according to either the process (1), (2) or (3) described below.

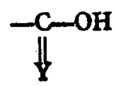
Process (1):

A process comprising reacting a compound represented by the general formula (II),

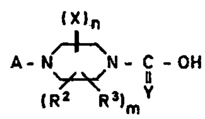


(II)

with a reactive derivative in the



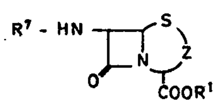
group (hereinafter refered to as " (thio)carboxyl group ") of a compound represented by the general formula (III),



(III)

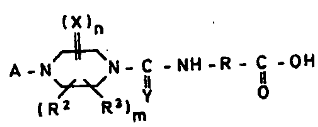
Process (2):

A process comprising reacting a compound represented by the general formula (IV),



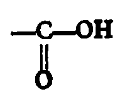
(IV)

with a compound represented by the general formula (V),



(V)

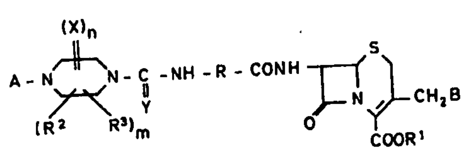
or with a reactive derivative in the



group (hereinafter referred to as " carboxyl group ") of the compound of formula (V).

Process (3):

A process comprising reacting a compound represented by the general formula (VI),



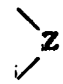
(VI)

with a compound represented by the general formula (VII),

$$R^8M \qquad \text{(VII)}$$

or with a tertiary amine.

In the above-mentioned formulas (II) to (VI), R, R^1, R^2, R^3, R^4, X, m, n, A, Y and



are as defined above; and R^7 represents a hydrogen atom, a silicon-containing group or a phosphorus-containing group, these silicon-containing and phosphorus-containing groups having the same meanings as mentioned above for R^1.

In the aforesaid formula (VI), B represents a substituent capable of being easily replaced by a nucleophilic reagent, and includes, for example, halogen atoms such as chlorine or bromine; lower alkanoyloxy groups such as formyloxy, acetoxy, propionyloxy, butyryloxy or pivaloyloxy; arylcarbonyloxy groups such as benzoyloxy or naphthoyloxy; arylcarbonylthio groups such as benzoylthio or naphthoylthio; carbamoyloxy groups; heteroaromatic amine N-oxide thio groups having a thio-group on the carbon atom adjacent to the N-oxide group in the molecule, such as pyridine-1-oxide-2-ylthio or pyridazine-1-oxide-6-ylthio. Each of the groups mentioned above for B may be substituted by any of such substituents as, halogen atoms, nitro groups alkyl groups, alkoxy groups, alkylthio groups or acyl groups.

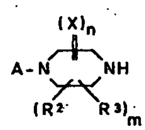
In formula (VII), R^8 represents a cyano group, an azido group or an organic group linked through O, N or S, and this organic group is the same as mentioned above for R^4.

In the formula (VII), M represents a hydrogen atom, an alkali metal or an alkaline earth metal. The tertiary amine used in the process (3) includes pyridine, quinoline, isoquinoline or pyrimidine. These tertiary amines may be substituted by various substituents such as halogen, lower alkyl or carbamoyl.

As the compound (II), there may be used any of D-isomer, L-isomer or racemic compound.

As the reactive derivative of the (thio)carboxyl group of the compound of formula (II), there is used a reactive derivative of a carboxylic acid which is ordinarily employed for the synthesis of acid amide compounds. Examples of the reactive derivative are acid halides, acid azides, acid cyanides, mixed acid anhydrides, active esters or active amides. Particularly preferable examples thereof are acid halides such as acid chlorides or acid bromides, and active esters such as cyanomethyl ester or trichloromethyl ester.

The reactive derivative of the (thio)carboxyl group of the compound of formula (III) can be easily obtained by reacting, for example, an oxopiperazine or thioxopiperazine of formula (VIII) synthesized according to the process of the literature references described below, with phosgene, thiophosgene, or trichloromethyl ester of chloroformic acid,



(VIII)

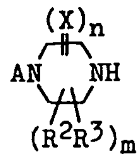
wherein A, X, R^2, R^3, m and n are as defined previously.

Literature references:

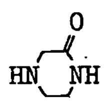
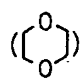
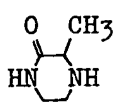
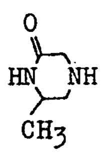
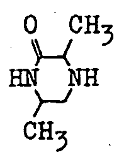
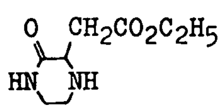
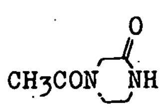
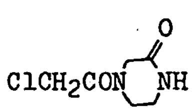
V. G. Granik, Khim-Farm. Zh., I(4), 16—19 (1967) (Russ);
Samuel R. Aspinall, J. An. Chem. Soc., 62, 1202—4 (1940);
Kuniyoshi MASUZAWA, Pharm. Bull. (Japan), *38* 2078—2081 (1966);
Arthur P. Phillips, Ger. 1135472, Aug. 30 (1962);
J. L. Riebsomer, J. Org. Chem., *15* 68—73 (1950);
Jongkees, Rec. trav. Chim., *27* 305;
Patric T. Izzo, J. Am. Chem. Soc., *81* 4668—4670 (1959); and
B. H. Chase & A. M. Downes, J. Chem. Soc., 3874—3877 (1953).

Concrete examples of the compound of formula (VIII) and the reactive derivative of (thio)carboxyl group of the compound of formula (III) are as set forth in Table 1 and Table 2, respectively, but it is needless to say that these are not limitative.

Table 1

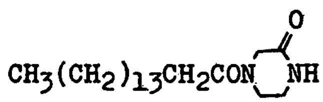
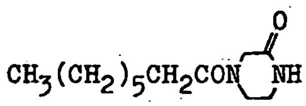
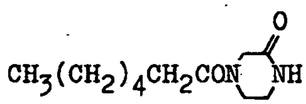
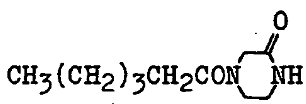
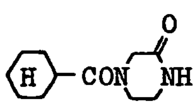
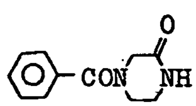
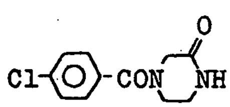
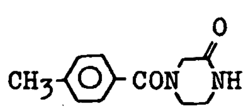
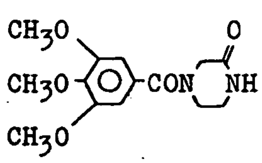


(VIII)

Compound	m.p. (recrystallization solvent)	IR (cm^{-1})
	136°C ()	$\nu_{C=O}$ 1640 ν_{NH} 3450 - 3250
	b.p. 143°C/1 mmHg oily material	$\nu_{C=O}$ 1650 ν_{NH} 3300 - 3200
	b.p. 122 - 125°C/2 mmHg 140 - 141°C (IPA)	$\nu_{C=O}$ 1650 - 1630 ν_{NH} 3260, 3170
	85 - 86°C (IPA - IPE)	$\nu_{C=O}$ 1660 - 1620
	105 - 106°C (AcOEt)	$\nu_{C=O}$ 1710, 1640 ν_{NH} 3300, 3190
	112 - 113°C ()	$\nu_{C=O}$ 1645, 1625 ν_{NH} 3380, 3220
	129 - 130°C (IPA)	$\nu_{C=O}$ 1650, 1630 ν_{NH} 3270

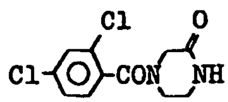
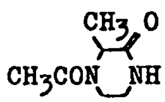
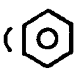
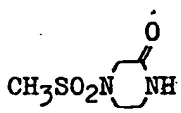
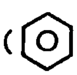
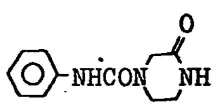
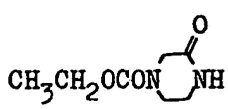
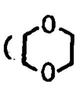
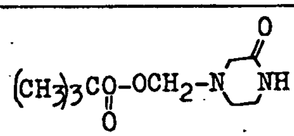
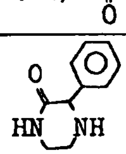
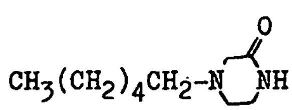
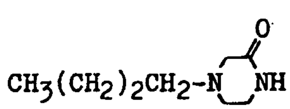
- cont'd -

Table 1 (Cont'd)

	134 - 135°C (IPA)	$\nu_{C=O}$ 1660-1630 ν_{NH} 3280
	96 - 97°C (CCl_4)	$\nu_{C=O}$ 1670, 1640 ν_{NH} 3200
	80 - 81°C (IPE)	$\nu_{C=O}$ 1660, 1620 ν_{NH} 3250
	83 - 84°C (IPE)	$\nu_{C=O}$ 1660, 1620 ν_{NH} 3250
	99 - 100°C (CCl_4)	$\nu_{C=O}$ 1660, 1620 ν_{NH} 3250
	203 - 205°C (IPA)	$\nu_{C=O}$ 1670, 1620 ν_{NH} 3250
	91 - 93°C (IPA)	$\nu_{C=O}$ 1640, 1600 ν_{NH} 3250
	146 - 148°C (IPA)	$\nu_{C=O}$ 1650, 1620 ν_{NH} 3200
	118 - 120°C (IPA)	$\nu_{C=O}$ 1660, 1620 ν_{NH} 3200
	182 - 185°C (IPA)	$\nu_{C=O}$ 1670, 1600 ν_{NH} 3200

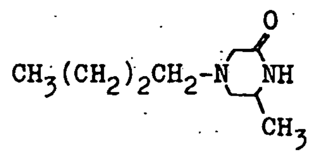
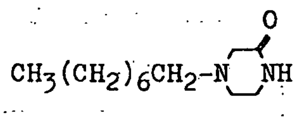
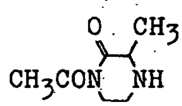
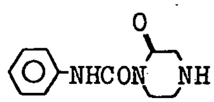
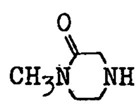
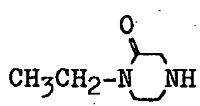
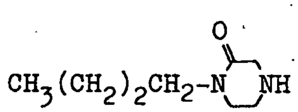
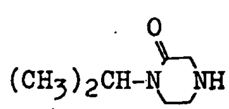
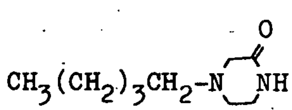
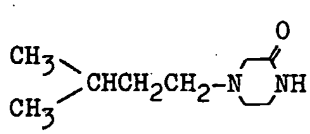
- cont'd -

Table 1 (Cont'd)

	Oily material	$\nu_{C=O}$ 1650, 1620 ν_{NH} 3200
	124 - 126°C ()	$\nu_{C=O}$ 1650, 1630 ν_{NH} 3225
	167 - 168°C (EtOH)	$\nu_{C=O}$ 1680 ν_{NH} 3200 $\nu_{SO_2N<}$ 1310, 1140
	176 - 179°C ()	$\nu_{C=O}$ 1680, 1650, 1620 ν_{NH} 3300
	85 - 88°C (AcOEt)	$\nu_{C=O}$ 1660, 1640 ν_{NH} 3300, 3200
	81 - 82°C ()	$\nu_{C=O}$ 1690 - 1650 ν_{NH} 3200, 3050
	189 - 190°C (IPA)	$\nu_{C=O}$ 1650, 1620 ν_{NH} 3250
	136 - 138°C (Acetone)	$\nu_{C=O}$ 1660 ν_{NH} 3200
	Oily material	$\nu_{C=O}$ 1650 - 1630 ν_{NH} 3270
	Oily material	ν_{NH} 3250 $\nu_{C=O}$ 1650 - 1630

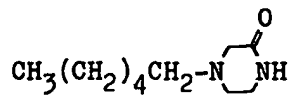
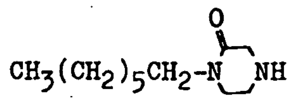
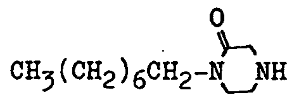
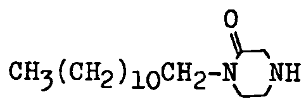
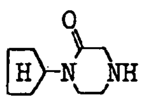
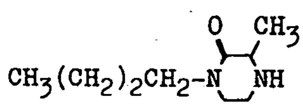
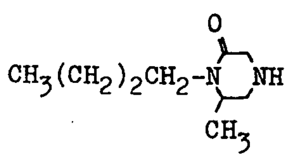
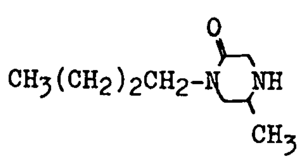
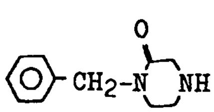
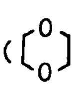
- cont'd -

Table 1 (Cont'd)

	Oily material	$\nu_{C=O}$ 1650 - 1620
	Oily material	ν_{NH} 3270 $\nu_{C=O}$ 1650 - 1630 Hydrochloride $\nu_{C=O}$ 1680 ν_{NH} 3200, 3080
	Oily material	$\nu_{C=O}$ 1680 ν_{NH} 3300
	Oily material	$\nu_{C=O}$ 1720, 1640 ν_{NH} 3300
	b.p. 104°C/4 mmHg	$\nu_{C=O}$ 1620 ν_{NH} 3275
	Oily material	$\nu_{C=O}$ 1610 ν_{NH} 3250
	Oily material	$\nu_{C=O}$ 1610 ν_{NH} 3250
	Oily material	$\nu_{C=O}$ 1610 ν_{NH} 3400 - 3200
	Oily material	$\nu_{C=O}$ 1620 ν_{NH} 3270
	Oily material	$\nu_{C=O}$ 1620 ν_{NH} 3270

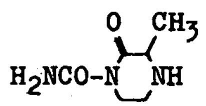
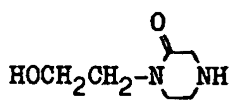
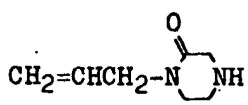
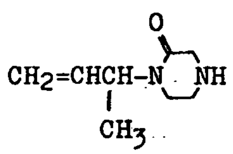
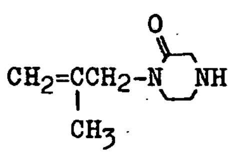
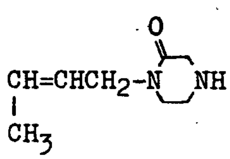
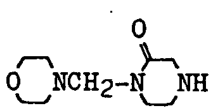
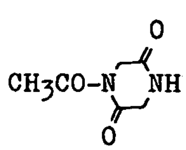
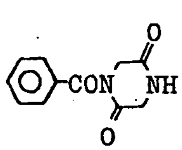
- cont'd -

Table 1 (Cont'd)

	Oily material	$\nu_{C=O}$ 1620 ν_{NH} 3270
	Oily material	$\nu_{C=O}$ 1620 ν_{NH} 3270
	Oily material	$\nu_{C=O}$ 1620 ν_{NH} 3270
	Oily material	$\nu_{C=O}$ 1620 ν_{NH} 3270
	Oily material	$\nu_{C=O}$ 1620 ν_{NH} 3300
	Oily material	$\nu_{C=O}$ 1630 ν_{NH} 3300
	Oily material	$\nu_{C=O}$ 1630 ν_{NH} 3300
	Oily material	$\nu_{C=O}$ 1630 ν_{NH} 3200
	157 - 158°C ()	$\nu_{C=O}$ 1630 ν_{NH} 3300

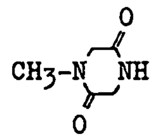
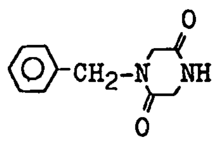
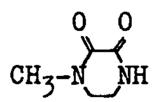
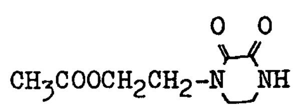
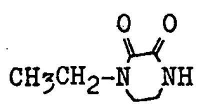
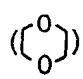
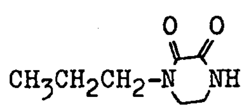
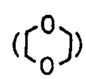
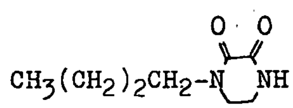
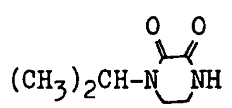
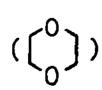
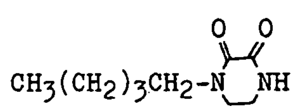
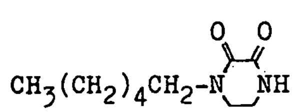
- cont'd -

Table 1 (Cont'd)

	Oily material	$\nu_{C=O}$ 1700 ν_{NH} 3400 - 3250
	b.p. 183 - 185°C/2mmHg	$\nu_{C=O}$ 1620
	Oily material	$\nu_{C=O}$ 1650 ν_{NH} 3300
	Oily material	$\nu_{C=O}$ 1620 ν_{NH} 3300
	Oily material	$\nu_{C=O}$ 1640 ν_{NH} 3300
	Oily material	$\nu_{C=O}$ 1660 ν_{NH} 3350
	Oily material	$\nu_{C=O}$ 1630 ν_{NH} 3300
	184 - 185°C (EtOH)	$\nu_{C=O}$ 1690 - 1650 ν_{NH} 3190, 3050
	177 - 178°C (EtOH)	$\nu_{C=O}$ 1680 - 1650 ν_{NH} 3190, 3050

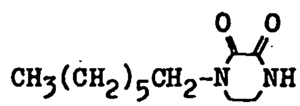
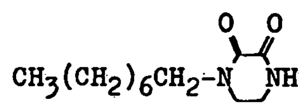
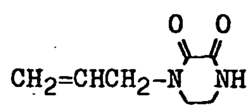
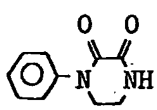
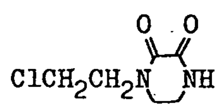
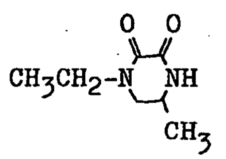
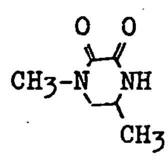
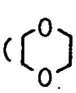
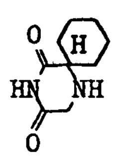
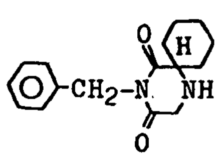
- cont'd -

Table 1 (Cont'd)

	142 - 143°C (IPA)	$\nu_{C=O}$ 1680 - 1620 ν_{NH} 3200
	209°C (IPA)	$\nu_{C=O}$ 1660 - 1630 ν_{NH} 3230
	158°C (IPA)	$\nu_{C=O}$ 1695, 1660 ν_{NH} 3220
	Oily material	$\nu_{C=O}$ 1730 - 1650 ν_{NH} 3300 - 3200
	124°C ()	$\nu_{C=O}$ 1680, 1650 ν_{NH} 3250
	98 - 100°C ()	$\nu_{C=O}$ 1680, 1650 ν_{NH} 3200, 3100
	111 - 113°C (CCl_4)	$\nu_{C=O}$ 1695, 1670 ν_{NH} 3240, 3150
	166 - 167°C ()	$\nu_{C=O}$ 1650 ν_{NH} 3300 - 3200
	104 - 106°C (IPE)	$\nu_{C=O}$ 1700, 1660 ν_{NH} 3200, 3100
	111 - 115°C (IPE)	$\nu_{C=O}$ 1700, 1660 ν_{NH} 3200, 3100

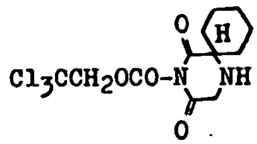
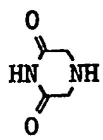
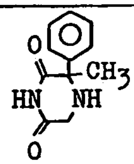
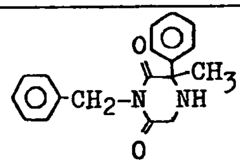
- cont'd -

Table 1 (Cont'd)

	112 - 115°C (IPE)	$\nu_{C=O}$ 1700, 1660 ν_{NH} 3200, 3100
	116 - 120°C (IPE)	$\nu_{C=O}$ 1700, 1660 ν_{NH} 3225, 3100
	136 - 137°C (Acetone)	$\nu_{C=O}$ 1680, 1655 ν_{NH} 3200, 3100
	202 - 204°C (IPA)	$\nu_{C=O}$ 1690, 1645 ν_{NH} 3260
	128 - 129°C (EtOH)	$\nu_{C=O}$ 1700 - 1650 ν_{NH} 3200 - 3100
	127 - 128°C (AcOEt)	$\nu_{C=O}$ 1660 ν_{NH} 3200, 3080
	146 - 147°C ()	$\nu_{C=O}$ 1660 ν_{NH} 3200, 3100
	183 - 185°C (EtOH)	$\nu_{C=O}$ 1720, 1660 ν_{NH} 3320, 3175, 3050
	96 - 99°C (IPA-n-Hexane)	$\nu_{C=O}$ 1720, 1660 ν_{NH} 3330

– cont'd –

Table 1 (Cont'd)

	143 - 146°C (IPA)	$\nu_{C=O}$ 1765, 1720, 1680 ν_{NH} 3350
	210 - 212°C (MeOH)	$\nu_{C=O}$ 1680 ν_{NH} 3380, 3290, 3070
	132 - 133°C (EtOH)	$\nu_{C=O}$ 1715, 1685 ν_{NH} 3275, 3170
	98 - 100°C (IPA)	$\nu_{C=O}$ 1715, 1665 ν_{NH} 3360

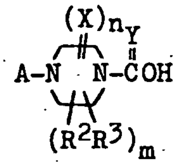
Note: IPA = $(CH_3)_2CHOH$

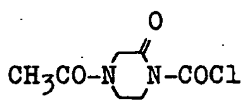
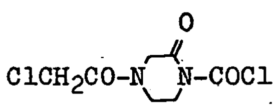
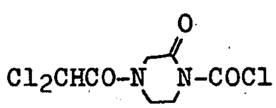
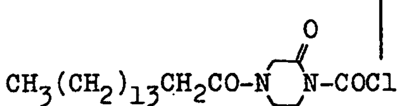
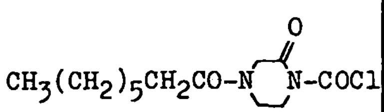
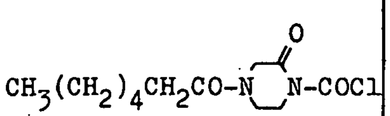
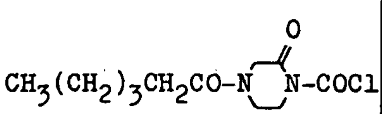
IPE = $(CH_3)_2CHOCH(CH_3)_2$

AcOEt = $CH_3COOCH_2CH_3$

EtOH = CH_3CH_2OH

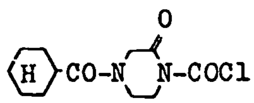
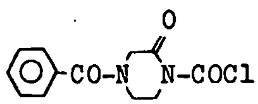
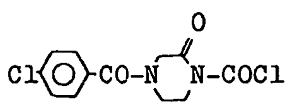
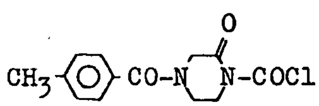
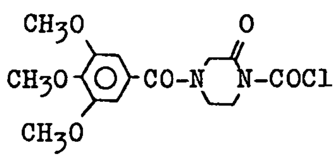
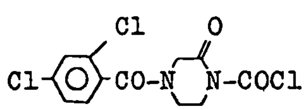
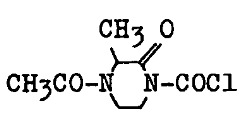
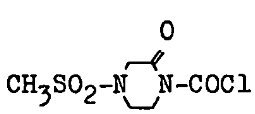
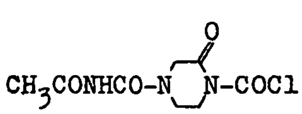
Table 2

Reactive derivatives of  (III)

Compound	Physical property	I.R. (cm^{-1})
	Oily material	$\nu_{C=0}$ 1790, 1710, 1640
	"	$\nu_{C=0}$ 1790, 1730 - 1650
	"	$\nu_{C=0}$ 1790, 1730 - 1650
	"	$\nu_{C=0}$ 1740, 1660, 1640
	"	$\nu_{C=0}$ 1740, 1680 - 1640
	"	$\nu_{C=0}$ 1740, 1680 - 1640
	"	$\nu_{C=0}$ 1790, 1710, 1640

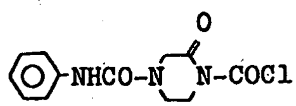
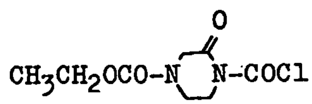
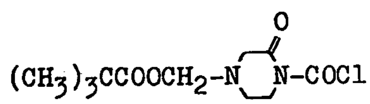
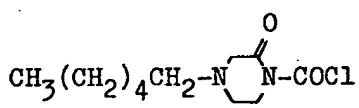
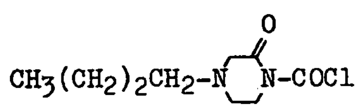
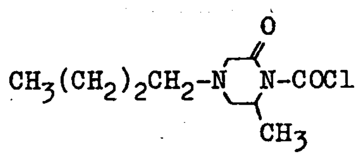
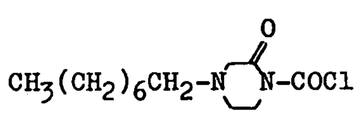
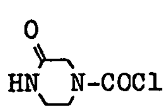
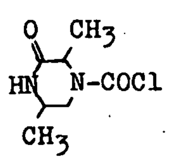
- cont'd -

Table 2 (Cont'd)

	Oily material	$\nu_{C=O}$ 1790, 1730, 1640
	"	$\nu_{C=O}$ 1740, 1660, 1630
	"	$\nu_{C=O}$ 1740, 1640
	"	$\nu_{C=O}$ 1730, 1650
	"	$\nu_{C=O}$ 1740, 1640
	"	$\nu_{C=O}$ 1720, 1640
	"	$\nu_{C=O}$ 1790, 1710, 1640
	"	$\nu_{C=O}$ 1790, 1700 ν_{SO_2} 1320, 1140
	"	$\nu_{C=O}$ 1790, 1720 - 1660

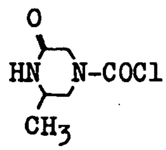
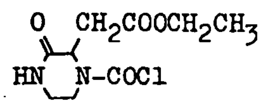
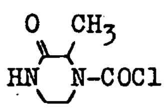
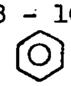
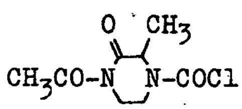
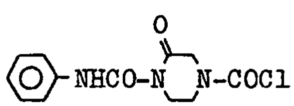
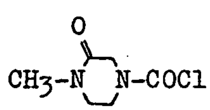
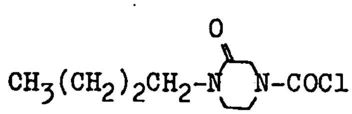
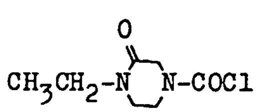
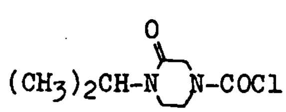
- cont'd -

Table 2 (Cont'd)

	Oily material	$\nu_{C=O}$ 1740, 1720, 1650
	"	$\nu_{C=O}$ 1750, 1720, 1640
	"	$\nu_{C=O}$ 1740 - 1720, 1670
	"	$\nu_{C=O}$ 1790, 1720
	"	$\nu_{C=O}$ 1790, 1720
	"	$\nu_{C=O}$ 1790, 1720
	"	$\nu_{C=O}$ 1790, 1720
	m.p. 115 - 116°C (decomp.) (from )	$\nu_{C=O}$ 1720, 1660
	Crystal	$\nu_{C=O}$ 1730, 1670

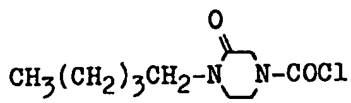
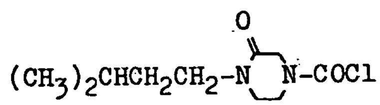
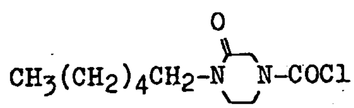
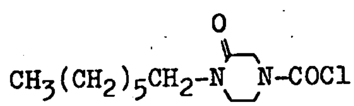
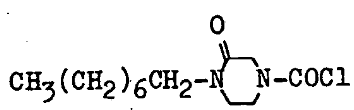
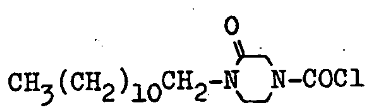
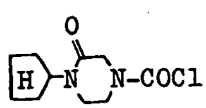
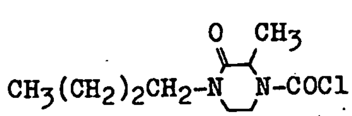
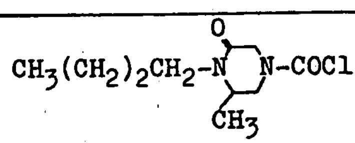
- cont'd -

Table 2 (Cont'd)

	Crystal	$\nu_{C=O}$ 1720, 1660
	m.p. 59 - 60°C (from IPE)	$\nu_{C=O}$ 1710 - 1730, 1660
	m.p. 98 - 100°C (from )	$\nu_{C=O}$ 1725, 1650
	Oily material	$\nu_{C=O}$ 1720, 1690
	"	$\nu_{C=O}$ 1790, 1740 - 1700
	"	$\nu_{C=O}$ 1710, 1630
	"	$\nu_{C=O}$ 1730, 1650
	"	$\nu_{C=O}$ 1730, 1650
	"	$\nu_{C=O}$ 1720, 1640

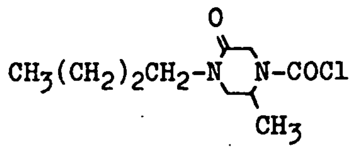
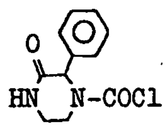
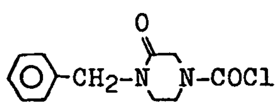
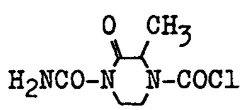
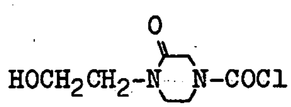
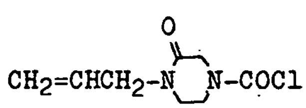
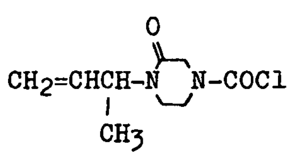
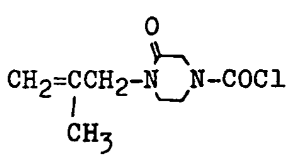
- cont'd -

Table 2 (Cont'd)

	Oily material	$\nu_{C=O}$ 1730, 1640
	"	$\nu_{C=O}$ 1720, 1640
	"	$\nu_{C=O}$ 1730, 1640
	"	$\nu_{C=O}$ 1730, 1640
	"	$\nu_{C=O}$ 1720, 1640
	"	$\nu_{C=O}$ 1720, 1640
	"	$\nu_{C=O}$ 1730, 1640
	"	$\nu_{C=O}$ 1730, 1640
	"	$\nu_{C=O}$ 1720, 1640

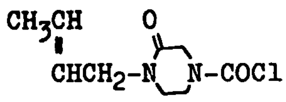
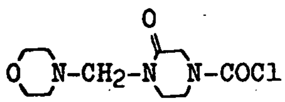
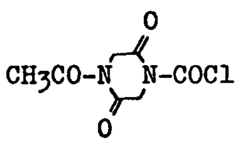
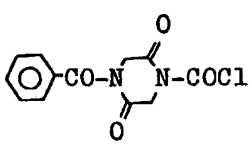
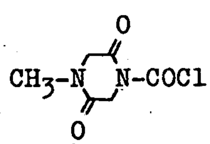
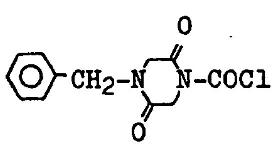
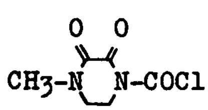
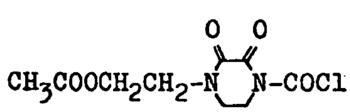
- cont'd -

Table 2 (Cont'd)

	Oily material	$\nu_{C=O}$ 1730, 1650
	m.p. 105 - 107°C	$\nu_{C=O}$ 1730, 1650
	Oily material	$\nu_{C=O}$ 1720, 1645
	"	$\nu_{C=O}$ 1700 - 1740
	"	$\nu_{C=O}$ 1730, 1660 - 1630
	"	$\nu_{C=O}$ 1720, 1640
	"	$\nu_{C=O}$ 1730, 1650
	"	$\nu_{C=O}$ 1730, 1650

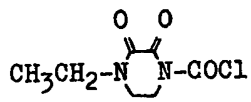
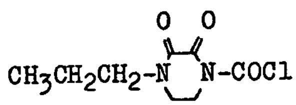
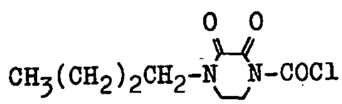
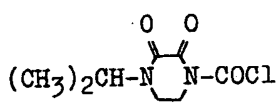
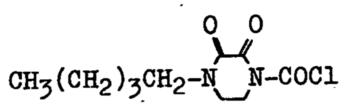
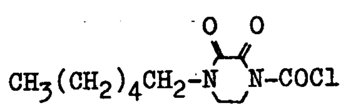
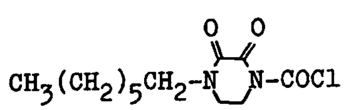
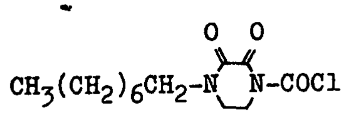
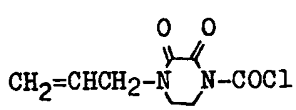
- cont'd -

Table 2 (Cont'd)

 (trans-)	Oily material	$\nu_{C=O}$ 1730, 1650
	m.p. 150°C (decomp.)	$\nu_{C=O}$ 1670, 1720
	Oily material	$\nu_{C=O}$ 1790, 1720 - 1670
	"	$\nu_{C=O}$ 1790, 1710, 1670
	"	$\nu_{C=O}$ 1790, 1710 - 1660
	"	$\nu_{C=O}$ 1790, 1710 - 1660
	m.p. 94 - 95°C (decomp.) (from CH_2Cl_2-Et_2O)	$\nu_{C=O}$ 1790, 1680
	Oily material	$\nu_{C=O}$ 1790, 1720, 1670

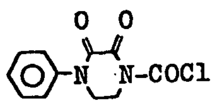
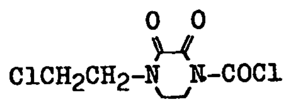
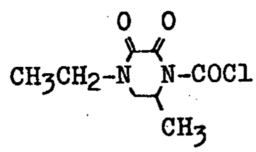
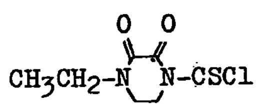
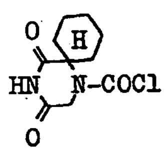
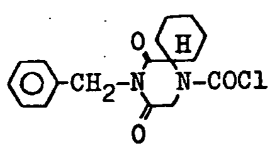
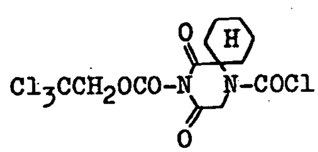
- cont'd -

Table 2 (Cont'd)

	m.p. 95 - 96°C (decomp.) (from AcOBu)	$\nu_{C=O}$ 1780, 1660
	Oily material	$\nu_{C=O}$ 1780, 1710 - 1640
	"	$\nu_{C=O}$ 1780, 1660
	m.p. 130 - 131°C (decomp.)	$\nu_{C=O}$ 1780, 1660
	Oily material	$\nu_{C=O}$ 1790, 1720 - 1665
	"	$\nu_{C=O}$ 1780, 1720 → 1640
	"	$\nu_{C=O}$ 1780, 1720 - 1640
	"	$\nu_{C=O}$ 1780, 1720 - 1640
	Crystal	$\nu_{C=O}$ 1775, 1660 - 1620

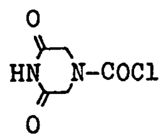
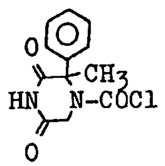
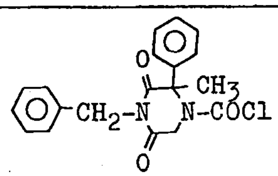
- cont'd -

Table 2 (Cont'd)

	Crystal	$\nu_{C=0}$ 1785, 1720 - 1650
	Oily material	$\nu_{C=0}$ 1790, 1720, 1680
	m.p. 65 - 70°C (decomp.)	$\nu_{C=0}$ 1785, 1680
	m.p. 100 - 101°C (decomp.)	$\nu_{C=0}$ 1725, 1675
	m.p. 180 - 181°C	$\nu_{C=0}$ 1740, 1695
	m.p. 160 - 165°C	$\nu_{C=0}$ 1740, 1670
	Oily material	$\nu_{C=0}$ 1800, 1750, 1710

- cont'd -

Table 2 (Cont'd)

	m.p. 185 - 187°C (decomp.)	$\nu_{C=O}$ 1730, 1690
	Oily material	$\nu_{C=O}$ 1750, 1710 - 1685
	"	$\nu_{C=O}$ 1735, 1725, 1710, 1675

Note: $Et_2O = CH_3CH_2OCH_2CH_3$

$AcOBu = CH_3COO(CH_2)_3CH_3$

The compound represented by the general formula (V) can be easily obtained by reacting, for example, a salt with an alkali metal, an alkaline earth metal or a nitrogen-containing organic base of an amino acid (IX) (any of D-isomer, L-isomer and racemic compound) represented by the general formula (IX)

$$H_2N—R—COOH \qquad (IX)$$

wherein R is as defined previously, with a reactive derivative in the (thio)carboxyl group of a compound represented by the general formula (III) in a solvent inert to the reaction in the presence of an acid-binding agent. Preferable examples of the compound of formula (V) are D-isomers, L-isomers and racemic compounds of the following compounds, though it is needless to say that the examples are not limitative:

α - (4 - Acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Chloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Dichloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Palmitoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Caproyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Capryloyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Enanthoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Cyclohexanecarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Benzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - p - Chlorobenzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - p - Methoxybenzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - [4 - (3,4,5 - Trimethoxybenzoyl) - 2 - oxo - 1 - piperazinocarbonylamino]-phenylacetic acid

α - [4 - (2,4 - Dichlorobenzoyl) - 2 - oxo - 1 - piperazinocarbonylamino]phenylacetic acid

α - (4 - Acetyl - 3 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Phenylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Ethoxycarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Pivaloyloxymethyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Hexyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Butyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Butyl - 6 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Octyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (3 - Oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (2,5 - Dimethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (5 - Methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (2 - Ethoxycarbonylmethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (2 - Methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Acetyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Phenylaminocarbonyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Isopropyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Pentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - iso - Pentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Hexyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Heptyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Octyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Dodecyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Cyclopentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (2 - Methyl - 4 - n - butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Butyl - 5 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - n - Butyl - 6 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (2 - Phenyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Benzyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Carbamoyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - β - Hydroxyethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Allyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - α - Methylallyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - β - Methylallyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - [4 - (Trans - 2 - butenyl) - 3 - oxo - 1 - piperazinocarbonylamino]phenylacetic acid

α - (4 - Morpholinomethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Ethyl - 3 - oxo - 1 - piperazinocarbonylamino)propionic acid

α - (4 - Acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Benzoyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Methyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Benzyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid

α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Acetoxyethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - n - Propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - n - Butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Isopropyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - n - Pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - n - Hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - n - Heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - n - Octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Allyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - β - Chloroethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Pyrrolidinoethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetic acid
α - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetic acid
α - (6 - Methyl - 4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4,6 - Dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)phenylacetic acid
α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexadienylacetic acid
α - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexadienylacetic acid
α - (4 - n - Propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexadienylacetic acid
α - (4 - n - Butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexadienylacetic acid
α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic acid
α - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic acid
α - (4 - n - Propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic acid
α - (4 - n - Butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic acid
α - (2,2 - Pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Benzyl - 2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - β,β,β - Trichloroethoxycarbonyl - 2,2 - pentamethylene - 3,5 - dioxo - 1-piperazinocarbonylamino)phenylacetic acid
α - (3,5 - Dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (2 - Methyl - 2 - phenyl - 3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Benzyl - 2 - methyl - 3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid
α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid

As the reactive derivative in the carboxyl group of the compound represented by the general formula (V), there is used a reactive derivative of a carboxylic acid which is ordinarily used in the synthesis of acid amides. Such reactive derivative includes, for example, acid halides, acid anhydrides, mixed acid anhydrides with organic or inorganic acids, active acid amides, acid cyanides or active esters. Particularly, acid chlorides, mixed acid anhydrides and active acid amides are preferable. Examples of the mixed acid anhydrides are mixed acid anhydrides with substituted acetic acids, alkyl carbonic acids, aryl carbonic acids and aralkyl carbonic acids; examples of the active esters are cyanomethyl esters, substituted phenyl esters, substituted benzyl esters or substituted thienyl esters; and examples of the active acid amides are N-acyl saccharins, N-acyl imidazoles, N-acyl benzoylamides, N,N-dicyclohexyl-N-acylureas or N-acyl sulfonamides.

Compounds of formula (VI) can be obtained by, for example, process (1) or (2).

Some of the compounds obtained by process (3) can further be used as the starting compounds in process (3). Any of D-, L- and racemic compounds of formula (VI) may be used.

The modes of practice of the processes (1), (2) and (3) are explained below.

The processes (1) and (2) may be carried out under substantially the same conditions. That is, the compound of formula (II) or (IV) is dissolved or suspended in at least one inert solvent selected from, for example, water, acetone, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide, methanol, ethanol, methoxyethanol, diethyl ether, isopropyl ether, benzene, toluene, methylene chloride, chloroform, ethyl acetate and methyl isobutyl ketone. The resulting solution or suspension is reacted with a reactive derivative of the compound of formula (III), or with the compound of formula (V) or a reactive derivative in the carboxyl group of the compound of formula (V) in the presence or absence of a base at a temperature in the range from −60° to 80°C., preferably from −40° to 30°C. The reaction time is ordinarily 5 minutes to 5 hours. Examples of the base used in the above reaction are inorganic bases such as alkali hydroxides, alkali hydrogencarbonates, alkali carbonates, or alkali acetates; tertiary amines such as trimethylamine, triethylamine, tributylamine, pyridine, N-methylpiperidine, N-methylmorpholine, lutidine and collidine; and secondary amines such as dicyclohexylamine or diethylamine. When the compound of formula (V) is used in the form of a free acid or salt in the process (2), the reaction of the process (2) may be effected in the presence of a dehydrating condensing agent such as N,N-dicyclohexyl carbodiimide, N-cyclohexyl-N′-morpholinoethyl carbodiimide, N,N′-diethyl carbodiimide, N,N′-carbonyl (2-methylimidazole), a trialkyl ester of phosphorous acid, ethyl ester of polyphosphoric acid, phosphorus oxychloride, phosphorus trichloride, 2-chloro-1,3,2-dioxaphospholane or oxazolyl chloride. The salt of the compound of formula (V) includes alkali metal salts, alkaline earth metal salts, ammonium salts, and salts with organic bases such as trimethylamine or dicyclohexylamine.

The process (3) is carried out in the manner described below.

When B in the formula (VI) is a group other than a hetero aromatic N-oxide thio group having a thio group on the carbon atom adjacent to the N-oxide group in the molecule, the compound of formula (VI) is reacted with the compound of formula (VII) or a tertiary amine in at least one solvent selected from, for example, water, methanol, ethanol, propanol, isopropanol, butanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, tetrahydrofuran, dioxane, acetonitrile, ethyl acetate, methoxyethanol, dimethoxyethane, dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform and a dichloroethane. The above-mentioned reaction is preferably effected in a strongly polar solvent such as water. In this case, the pH of the reaction solution is advantageously maintained at 2 to 10, preferably 4 to 8. The desired pH may be attained by addition of a buffer solution such as sodium phosphate. The reaction conditions are not particularly limited, though the reaction is ordinarily conducted at 0° to 100°C. over a period of at least several hours. When B in the formula (VI) is a hetero aromatic N-oxide thio group having a thio group on the carbon atom adjacent to the N-oxide group in the molecule, the compound of formula (VI) is reacted with the compound of formula (VII) in the above-mentioned solvent in the presence of a cupric compound. This reaction is particularly useful where an alcohol is used such as methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, n-butyl alcohol, benzyl alcohol or ethylene glycol as the compound of formula (VII). In this case, the reaction proceeds smoothly by using an excess of the alcohol per se to allow it to act as the reaction medium, too. The cupric compound used in this process includes organic and inorganic ones, such as cupric chloride, bromide, fluoride, nitrate, sulfate, borate, phosphate, cyanide, formate, acetate, propionate, citrate, tatarate, benzoate and salicylate. The amount of the cupric compound used is preferably 1/2 mole per mole of the compound of formula (VI). The reaction temperature and the reaction time may be varied depending upon the kinds of compound of formula (VI), cupric compound and compound of formula (VII), though they are usually selected from the range of 0° to 100°C and the range of several minutes to several days, respectively.

The reaction conditions to be adopted in the processes (1), (2) and (3) are not limited to those mentioned above, and can be properly varied depending upon the kinds of reaction reagents.

Further, the non-toxic salts of the general formula (I), in which R^1 is a salt-forming cation, can be easily obtained according to an ordinary procedure from compounds of the general formula (I), in which R^1 is a hydrogen atom or a blocking group.

Thus, among the compounds of formula (I) of the present invention, the penicillins can be easily obtained according to any of the aforesaid processes (1) and (2), while

the cephalosporins can be easily obtained according to either the aforesaid process (1), (2) or (3).

The present penicillins and cephalosporins include concretely the following compounds though are not restricted thereto. The following penicillins can be produced by any of the aforesaid processes (1) and (2), and the following cephalosporins can be produced by any of the aforesaid processes (1), (2) and (3).

Penicillins:

6 - [D(−) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - dichloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - enanthoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - cyclohexanecarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - acetyl - 3 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - hexyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - butyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - butyl - 6 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - octyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - pivaloyloxymethyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - palmitoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - capryloyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - caproyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - chloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - benzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - p - chlorobenzoyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - p - methoxybenzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - {D(−) - α - [4 - (3,4,5 - trimethoxybenzoyl) - 2 - oxo - 1 - piperazinocarbonylamino]phenylacetamido}penicillanic acid,

6 - {D(−) - α - [4 - (2,4 - dichlorobenzoyl) - 2 - oxo - 1 - piperazinocarbonylamino]phenylacetamido}penicillanic acid,

6 - [D(−) - α - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - phenylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - ethoxycarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - isopropyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - pentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - iso - pentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (2 - methyl - 4 - n - butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - n - butyl - 5 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - n - butyl - 6 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - benzyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - β - hydroxyethyl - 3 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - acetyl - 2 - methyl - 3 - oxo - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - carbamoyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (2,5 - dimethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (5 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicilanic acid,

6 - [D(—) - α - (2 - ethoxycarbonylmethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)propionamido]penicillanic acid,

6 - [D(—) - α - (4 - allyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - α - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - β - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - {D(—) - α - [4 - (trans - 2 - butenyl) - 3 - oxo - 1 - piperazinocarbonylamino]phenylacetamido}penicillanic acid,

6 - [D(—) - α - (4 - n - hexyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - n - heptyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - n - octyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - n - dodecyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - cyclopentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - phenylaminocarbonyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (2 - phenyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - morpholinomethyl - 3 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - benzoyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - methyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - benzyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(—) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(−) - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - acetoxyethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - allyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(−) - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(−) - α - (4 - β - chloroethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (6 - methyl - 4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4,6 - dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-cyclohexadienylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-cyclohexadienylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-1,4 - cyclohexadienylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-cyclohexadienylacetamido]penicillanic acid,

6 - [DL - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2-thienylacetamido]penicillanic acid,

6 - [DL - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienyl-acetamido]penicillanic acid,

6 - [DL - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperadinocarbonylamino) - 2-thienylacetamido]penicillanic acid,

6 - [DL - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2-thienylacetamido]penicillanic acid,

6 - [D(−) - α - (2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]-penicillanic acid,

6 - [D(−) - α - (2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - benzyl - 2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - β,β,β - trichloroethoxycarbonyl - 2,2 - pentamethylene - 3,5-dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - benzyl - 2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piper-azinocarbonylamino)phenylacetamido]penicillanic acid,

pivaloyloxymethyl 6 - [D(−) - α - (2 - methyl - 3 - oxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanate,

phthalidyl 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanate,

phthalidyl 6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
phthalidyl 6 - [D(−) - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
phthalidyl 6 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
methoxymethyl 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
methoxymethyl 6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
methoxymethyl 6 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
methoxymethyl 6 - [D(−) - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
methoxymethyl 6 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
pivaloyloxymethyl 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
pivaloyloxymethyl 6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
pivaloyloxymethyl 6 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
β - piperidinoethyl 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
β - piperidinoethyl 6 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,
β - morpholinoethyl 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate and
β - morpholinoethyl 6 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate.

Cephalosporins:
7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - n - heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,
7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,
7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - Δ^3-cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 6 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]-Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4,6 - dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3-cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)propionamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]-Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - azidomethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - oxadiazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [3 - (2,6 - dimethyl - 5 - oxo - 2,5 - dihydro - 1,2,4 - triazinyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-

acetamido] - 3 - [2 - (4 - methyloxazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino]phenylacetamido] - 3 - [2 - (4 - methylthiazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (pyridyl - 1 - oxide) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - (2 - thiazolinylthiomethyl) - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1 - methylimidazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - (2 - pyrimidinylthiomethyl) - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [3 - (6 - methylpyridazinyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [1 - (4 - methylpiperazino)thiocarbonylthiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (3 - methylisoxazolyl)carbonylthiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - ethoxythiocarbonylthiomethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethoxycarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - hexyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3-cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl]-Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]-3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3-cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacet-

amido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [D - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid, and

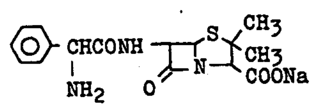
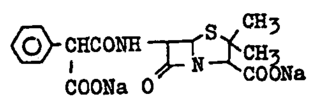
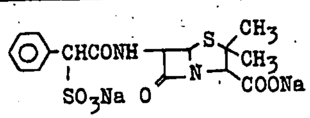
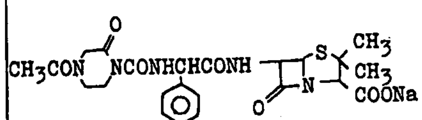
methoxymethyl 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylate.

The susceptible test of typical compounds among the compounds of the present invention are shown below.

(1) The minimum inhibitory concentrations (MIC) of the compounds against different standard strains are shown in Tables 3 and 4.

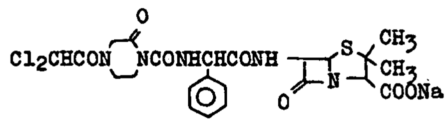
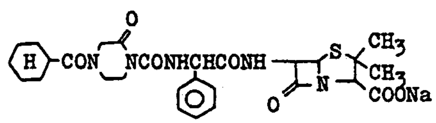
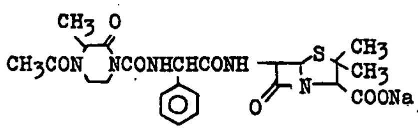
The minimum inhibitory concentration (MIC) was determined by the plate method disclosed in "Chemotherapy" (Japan), Vol. 16, (1968), pages 98—99. The culture medium used was a Heart infusion agar (pH 7.4). The number of the cells per plate used in the inoculum was 10^4 (10^6 cells/ml).

Table 3

Compound No.	Compound		Staphylococcus aureus 209p	Escherichia coli NIHJ	Pseudomonas aeruginosa I.F.O.	Klebsiella pneumoniae	Proteus vulgaris 3027
(Control)		(Sodium Ampicillin)	< 1.57	< 1.57	> 200	50	> 200
		(Sodium Carbenicillin)	< 1.57	< 1.57	50	> 200	< 1.57
		(Sodium Sulbenicillin)	3.13	1.57	50	> 200	0.79
1			< 1.57	< 1.57	25	12.5	3.13

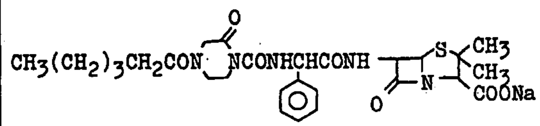
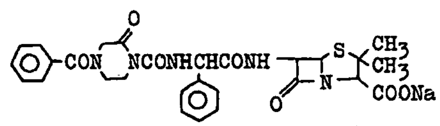
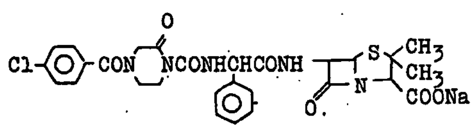
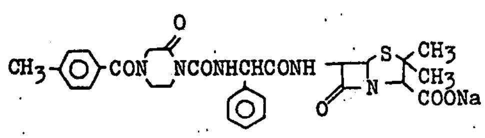
- cont'd -

Table 3 (Cont'd)

2		< 1.57	< 1.57	50	12.5	6.25
3		< 1.57	< 1.57	100	3.13	3.13
4		< 1.57	< 1.57	25	12.5	3.13
5		< 1.57	< 1.57	25	12.5	< 1.57

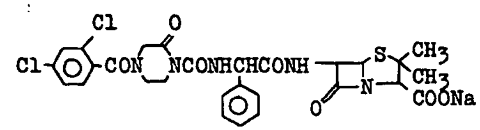
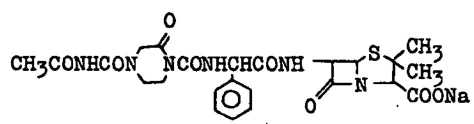
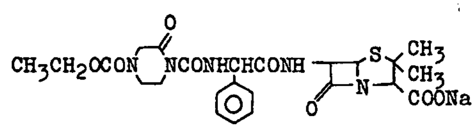
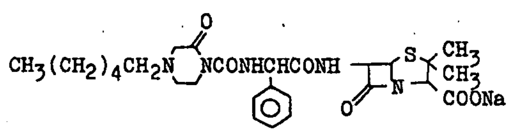
- cont'd -

Table 3 (Cont'd)

6		3.13	3.13	50	6.25	6.25
7		< 1.57	< 1.57	200	12.5	6.25
8		< 1.57	< 1.57	100	6.25	3.13
9		< 1.57	3.13	100	3.13	3.13

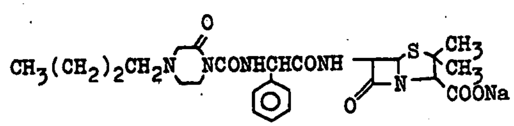
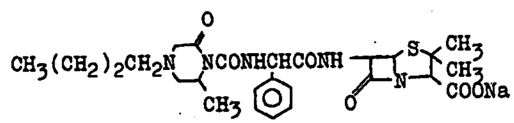
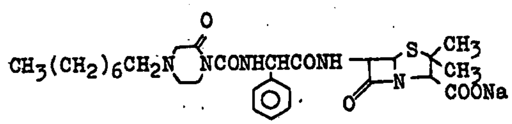
-cont'd -

Table 3 (Cont'd)

10		< 1.57	< 1.57	100	6.25	3.13
11		< 1.57	< 1.57	50	50	6.25
12		< 1.57	3.13	50	6.25	12.5
13		< 1.57	< 1.57	25	< 1.57	< 1.57

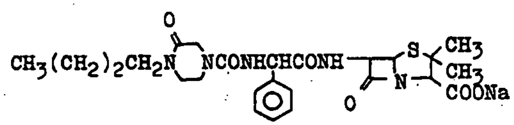
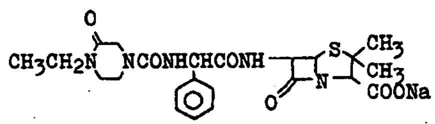
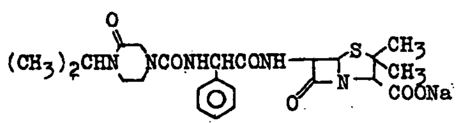
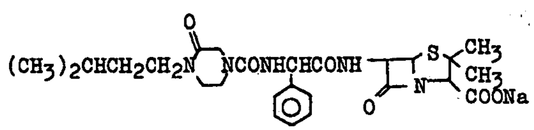
- cont'd -

Table 3 (Cont'd)

14		< 1.57	< 1.57	25	3.13	< 1.57
15		< 1.57	3.13	50	6.25	6.25
16		< 1.57	< 1.57	12.5	1.57	< 1.57
17		< 1.57	< 1.57	12.5	50	6.25

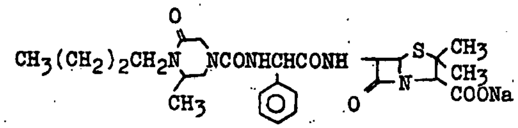
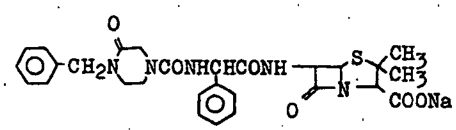
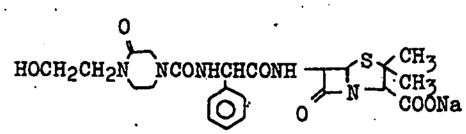
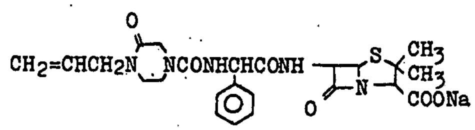
- cont'd -

Table 3 (Cont'd)

18		< 1.57	< 1.57	12.5	25	3.13
19		< 1.57	< 1.57	12.5	50	3.13
20		3.13	< 1.57	12.5	25	3.13
21		< 0.79	1.57	25	25	3.13

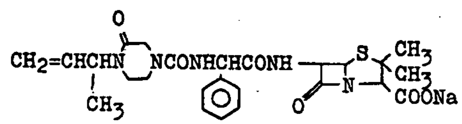
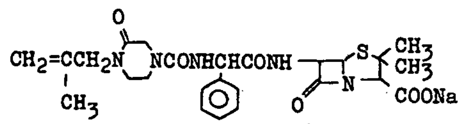
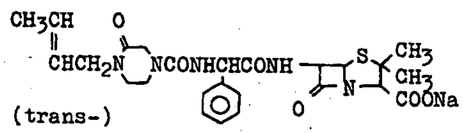
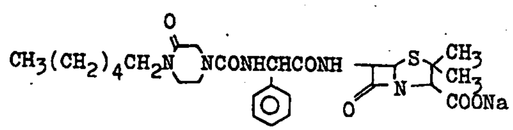
- cont'd -

Table 3 (Cont'd)

22		< 1.57	< 1.57	50	12.5	6.25
23		< 1.57	< 1.57	25	6.25	3.13
24		3.13	< 1.57	50	50	25
25		< 1.57	< 1.57	25	50	3.13

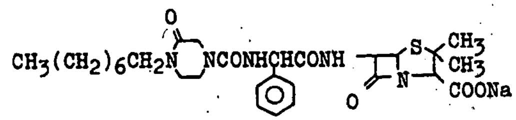
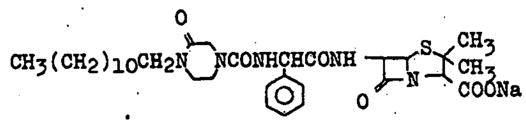
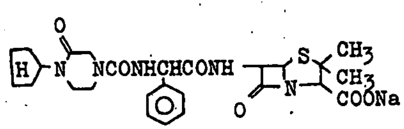
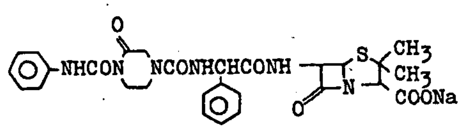
- cont'd -

Table 3 (Cont'd)

26		< 1.57	< 1.57	25	25	12.5
27		< 1.57	< 1.57	25	25	3.13
28	 (trans-)	< 1.57	< 1.57	25	25	3.13
29		3.13	< 1.57	12.5	3.13	3.13

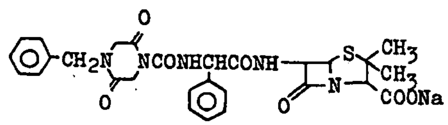
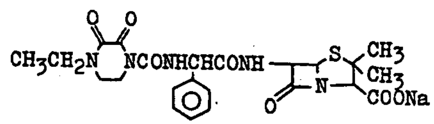
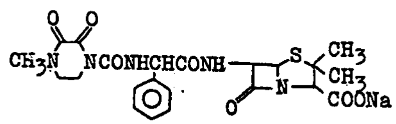
- cont'd -

Table 3 (Cont'd)

30		< 1.57	< 1.57	25	6.25	3.13
31		< 1.57	< 1.57	12.5	6.25	< 1.57
32		< 1.57	< 1.57	12.5	12.5	6.25
33		< 1.57	< 1.57	50	6.25	3.13

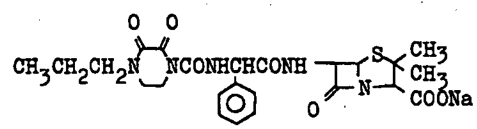
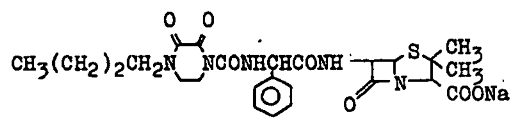
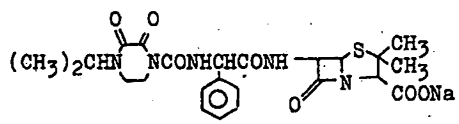
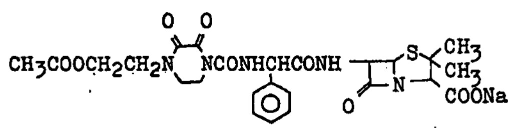
- cont'd -

Table 3 (Cont'd)

34		1.57	3.13	100	50	50
35		1.57	6.25	100	25	25
36		< 1.57	< 1.57	6.25	< 1.57	< 1.57
37		< 1.57	< 1.57	6.25	6.25	< 1.57

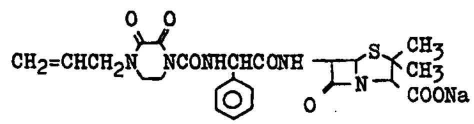
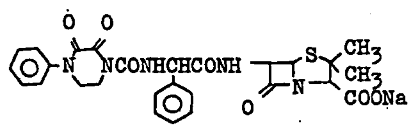
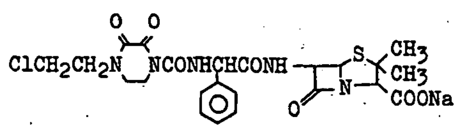
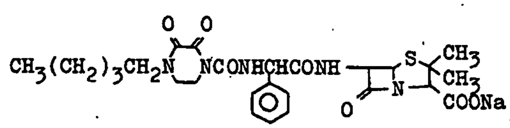
- cont'd -

Table 3 (Cont'd)

38		0.4	< 0.1	6.25	3.13	0.4
39		0.4	< 0.1	6.25	1.57	0.4
40		0.4	< 0.1	6.25	3.13	0.4
41		< 1.57	< 1.57	25	6.25	< 1.57

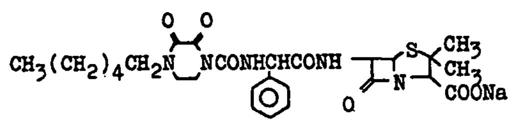
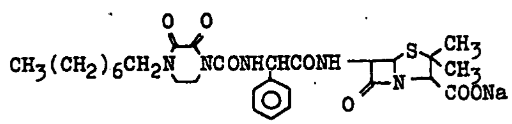
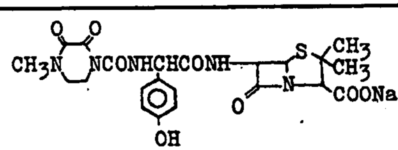
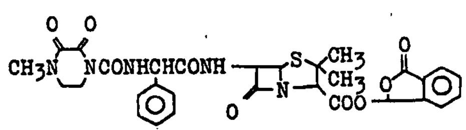
- cont'd -

Table 3 (Cont'd)

42		1.57	< 1.57	12.5	6.25	< 1.57
43		< 1.57	< 1.57	6.25	1.57	< 1.57
44		< 1.57	< 1.57	6.25	< 1.57	< 1.57
45		0.79	< 0.1	12.5	0.79	0.4

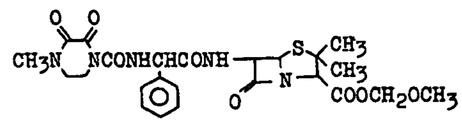
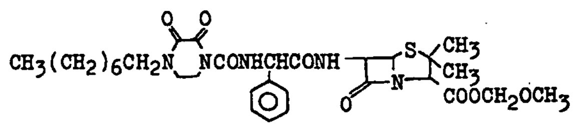
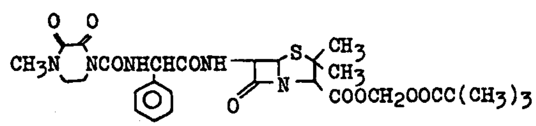
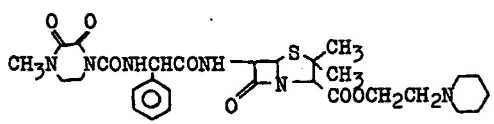
- cont'd -

Table 3 (Cont'd)

46		0.2	< 0.1	6.25	0.4	0.4
47		< 1.57	< 1.57	6.25	<1.57	< 1.57
48		< 0.4	< 0.4	6.25	25	< 0.4
49		< 0.4	0.79	12.5	12.5	1.57

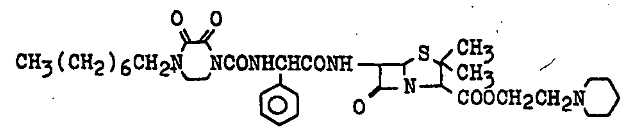
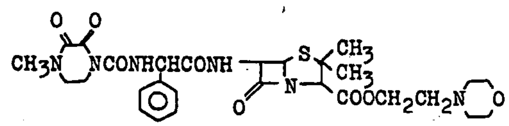
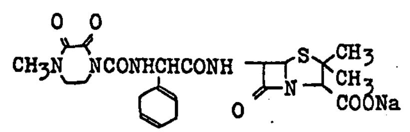
- cont'd -

Table 3 (Cont'd)

50		< 0.79	< 0.79	6.25	6.25	< 0.79
51		< 0.4	< 0.4	12.5	< 0.4	< 0.4
52		0.79	0.79	25	25	1.57
53		0.79	< 0.4	6.25	25	0.79

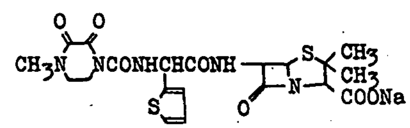
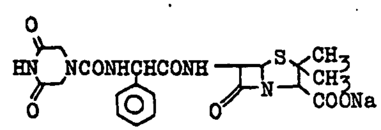
- cont'd -

Table 3 (Cont'd)

54		0.79	0.4	12.5	0.79	0.79
55		0.79	0.4	6.25	25	0.79
56		< 0.4	< 0.4	12.5	1.57	0.79
57		< 0.79	< 0.79	12.5	12.5	3.13

- cont'd -

Table 3 (Cont'd)

58		< 1.57	< 1.57	12.5	25	3.13
59		< 1.57	< 1.57	25	200	3.13

(Note) Sodium Carbenicillin and Sodium Sulbenicillin are regarded as preferable drugs at the level of this technical field, and hence are described for reference.

Table 4

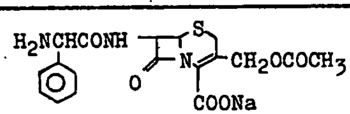
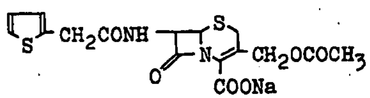
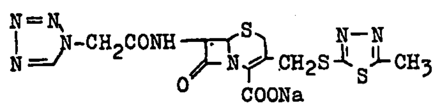
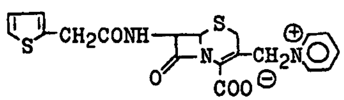
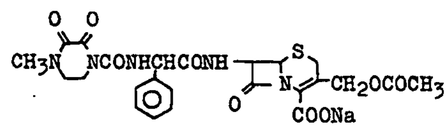
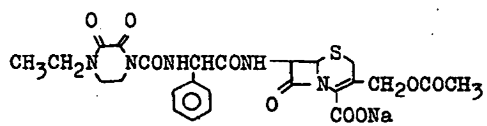
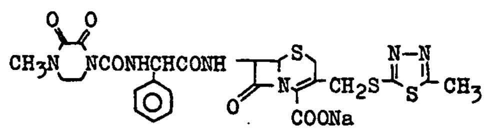
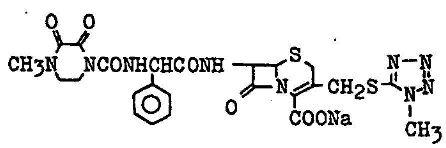
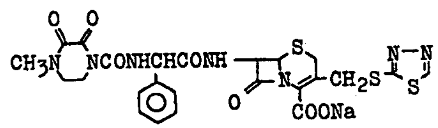
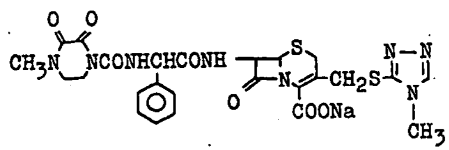
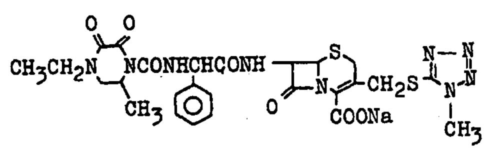
Compound No.	Compound		*Staphylococcus aureus* 209p	*Escherichia coli* NIHJ	*Pseudomonas aeruginosa* I.F.O.	*Klebsiella pneumoniae*	*Proteus vulgaris* 3027
(Control)		(Sodium Cephaloglycin)	< 1.57	< 1.57	> 200	100	< 1.57
		(Sodium Cephalothin)	< 1.57	< 1.57	> 200	100	< 1.57
		(Sodium Cephazolin)	< 1.57	< 1.57	> 200	200	1.57
		(Cephaloridine)	< 1.57	> 3.13	200	200	3.13

Table 4 (Cont'd)

60		0.79	< 0.1	25	3.13	3.13
61		< 0.79	< 0.79	25	3.13	3.13
62		0.79	< 0.1	50	1.57	3.13
63		< 0.79	< 0.79	25	< 0.79	1.57

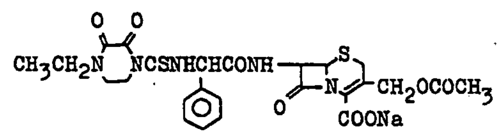
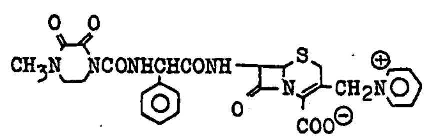
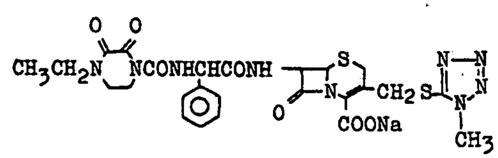
- cont'd -

Table 4 (Cont'd)

64		0.79	< 0.1	25	1.57	3.13
65		3.13	0.79	25	3.13	3.13
66		< 0.79	< 0.79	25	0.79	< 1.57

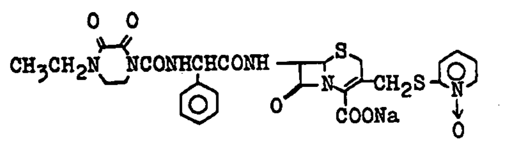
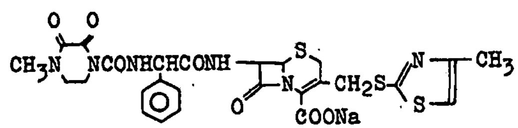
- cont'd -

Table 4 (Cont'd)

67		6.25	< 0.79	100	3.13	12.5
68		1.57	< 0.79	12.5	< 0.79	1.57
69		< 0.79	< 0.79	12.5	< 0.4	< 0.79

- cont'd

Table 4 (Cont'd)

70		< 0.79	1.57	100	1.56	< 0.79
71		< 0.79	< 0.79	50	1.56	< 0.79

(Note) Sodium Cephalothin, Sodium Cephazolin and Cephaloridine are regarded as preferable drugs at the level of this technical field, and hence are set forth for reference.

(2) The minimum inhibitory concentrations (MIC) of the compounds against clinical isolates of bacteria are shown in Tables 5 and 6.

MIC was determined in the same manner as in the preceding paragraph (1).

Table 5-1

	Compound	*Staphylococcus aureus*									
		MS 8619	MS 8588	MS 8713	MS 8596	MS 8684	F-1	F-2	F-3	F-4	F-5
Control	Sodium Ampicillin	< 0.4	6.25	3.13	1.56	1.56	12.5	0.79		12.5	50
Control	Sodium Carbenicillin	0.79	6.25	6.25	6.25	6.25	6.25	3.13	3.13	12.5	> 200
Control	Sodium Sulbenicillin	3.13	3.13	3.13	3.13	3.13	6.25	3.13	6.25	6.25	> 200
Compound No. 1		1.57	6.25	3.13	3.13	3.13	12.5	3.13		6.25	> 200
" 13		0.79	3.13	3.13	3.13	3.13	12.5	1.57		6.25	200
" 14		0.79	3.13	3.13	3.13	3.13	12.5	1.57		6.25	200
" 16		< 0.4	3.13	3.13	3.13	3.13	6.25	0.79		6.25	100
" 30		< 0.4	1.57	1.57	1.57	1.57	3.13	0.79	0.79	3.13	100

- cont'd -

Table 5-1 (Cont'd)

Compound No. 36	0.79	3.13	6.25	3.13	3.13	12.5	3.13	1.57	6.25	> 200
" 37	0.79	3.13	12.5	3.13	3.13	12.5	1.57	3.13	6.25	> 200
" 38	0.79	3.13	6.25	3.13	3.13	6.25	1.57	0.79	6.25	> 200
" 39	0.79	1.57	3.13	1.57	3.13	6.25	1.57	1.57	6.25	> 200
" 40	0.79	3.13	12.5	3.13	3.13	6.25	3.13	0.79	6.25	> 200
" 45	0.79	3.13	6.25	3.13	3.13	6.25	1.57	1.57	6.25	> 200
" 46	< 0.4	1.57	6.25	3.13	1.57	6.25	1.57	0.79	6.25	> 200
" 47	< 0.4	3.13	6.25	3.13	3.13	6.25	1.57	1.57	12.5	> 200

Table 5-2

Compound		*Escherichia coli*								
		GN 3481	GN 3435	GN 3452	GN 3465	GN 3611	K-1	K-2	K-3	K-4
Control	Sodium Ampicillin	6.25	3.13	6.25		>200	6.25	6.25	>200	12.5
	Sodium Carbenicillin	6.25	6.25	12.5	>200	>200	6.25	6.25	>200	12.5
	Sodium Sulbenicillin	12.5	6.25	12.5	>200	>200	6.25	12.5	>200	6.25
Compound No. 1		12.5	6.25	12.5	200		6.25	25	>200	12.5
" 13		6.25	3.13	3.13	25		3.13	6.25	100	6.25
" 14		6.25	6.25	6.25	50		3.13	12.5	200	6.25
" 16		3.13	1.57	1.57	12.5		1.57	3.13	50	3.13
" 30		25	12.5	25	50	>200	12.5	25	>200	12.5

- cont'd -

Table 5-2 (Cont'd)

Compound No. 36	3.13	1.57	3.13	100	> 200	3.13	3.13	>200	1.57
" 37	6.25	3.13	12.5	200	> 200	12.5	6.25	>200	3.13
" 38	3.13	0.79	3.13	50	> 200	3.13	3.13	>200	0.79
" 39	1.57	0.79	0.79	25	> 200	1.57	1.57	>200	0.79
" 40	1.57	0.79	1.57	50	> 200	1.57	3.13	>200	0.79
" 45	1.57	0.79	1.57	25	> 200	0.79	1.57	200	0.79
" 46	3.13	< 0.4	0.79	6.25	> 200	0.79	0.79	50	< 0.4
" 47	1.57	0.79	1.57	6.25	> 200	1.57	1.57	100	0.79

Table 5-3

Compound		Pseudomonas aeruginosa									
		GN 1035	GN 376	GN 82	GN 221	GN 1091	GN 2565	GN 2987	GN 163	GN 244	GN 383
Control	Sodium Ampicillin	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
Control	Sodium Carbenicillin	> 200	50	100	25	100	200	50	50	50	50
Control	Sodium Sulbenicillin	100	50	50	25	50	100	25	50	50	50
Compound No. 1		100	25	25	25	25	50	25	25	25	50
" 13		50	50	50	50	25	50	12.5	25	50	50
" 14		50	50	25	25	25	50	12.5	25	50	50
" 16		25	25	6.25	25	12.5	12.5	3.13	12.5	12.5	25
" 19		100	12.5	12.5	12.5	12.5	50	12.5	12.5	25	12.5
" 30		50	50	25	50	25	50	12.5	25	50	50

Table 5-3 (Cont'd)

Compound No. 36	25	6.25	6.25	3.13	6.25	25	12.5	6.25	12.5	6.25
" 37	50	12.5	6.25	6.25	12.5	25	25	12.5	50	25
" 38	12.5	3.13	3.13	6.25	3.13	12.5	6.25	3.13	6.25	6.25
" 39	12.5	6.25	3.13	3.13	3.13	12.5	3.13	3.13	6.25	6.25
" 40	25	3.13	6.25	6.25	6.25	12.5	3.13	6.25	6.25	6.25
" 45	50	25	12.5	3.13	12.5	25	12.5	12.5	25	25
" 46	50	25	6.25	12.5	12.5	12.5	6.25	6.25	12.5	25
" 47	25	50	12.5	25	12.5	25	12.5	12.5	25	50

Table 5-4

Compound		*Pseudomonas aernginosa*				*Klebsiella pneumoniae*			
		S-1	S-2	S-3	S-4	GN 4117	GN 4081	GN 3850	GN 917
Control	Sodium Ampicillin	> 200	> 200	> 200	> 200	> 200	> 200	50	25
	Sodium Carbenicillin	200	200	200	200	> 200	> 200		> 200
	Sodium Sulbenicillin	100	100	100	100	> 200	> 200	> 200	> 200
Compound No. 1		50	100	50	50	200	> 200	25	25
" 13		50	50	100	50	25	25	6.25	12.5
" 14		50	50	100	50	50	50	12.5	25
" 16		12.5	25	50	25	25	25	3.13	12.5
" 19		50	50	50	50	> 200	> 200	100	50
" 30		50	50	100	50	100	100	25	25

- cont'd -

Table 5-4 (Cont'd)

Compound No. 36	50	12.5	25	50	100	100	12.5	6.25
" 37	200	25	50	100	100	200	25	12.5
" 38	12.5	12.5	12.5	12.5	50	50	6.25	3.13
" 39	12.5	12.5	25	12.5	25	25	3.13	1.57
" 40	12.5	25	25	12.5	50	100	12.5	6.25
" 45	25	25	50	25	25	25	3.13	1.57
" 46	50	50	50	50	12.5	12.5	1.57	0.79
" 47	50	50	50	50	12.5	12.5	3.13	1.57

Table 5-5

Compound		*Shigella sonnei*		*Shigella flexneri*		*Salmonella typhi*		*Salmonella typhi-murium*	
		JS 11755	JS 11232	JS 11215	JS 11839	SL 2169	SL 819	SL 2136	SL 858
Control	Sodium Ampicillin	6.25	>200		1.57	0.78	1.56	>200	3.13
Control	Sodium Carbenicillin	12.5	>200	>200	12.5	3.13	6.25	>200	12.5
Control	Sodium Sulbenicillin	>200	>200	>200	12.5	1.57	6.25	>200	25
Compound No. 1		12.5	>200	100	3.13	6.25	6.25	>200	12.5
" 13		3.13	12.5	12.5	1.57	3.13	6.25	200	0.79
" 14		6.25	25	25	3.13	3.13	6.25	200	1.57
" 16		1.57	6.25	6.25	0.79	1.57	3.13	100	1.57

- cont'd -

Table 5-5 (Cont'd)

Compound No. 36	3.13	50	100	3.13	1.57	1.57	> 200	6.25
" 37	6.25	100	> 200	6.25	3.13	6.25	> 200	12.5
" 38	3.13	50	25	1.57	0.79	1.57	200	3.13
" 39	1.57	25	25	0.79	0.79	0.79	100	0.79
" 40	3.13	50	50	3.13	1.57	1.57	> 200	6.25
" 45	1.57	25	25	1.57	0.79	1.57	200	0.79
" 46	0.79	12.5	6.25	0.79	0.79	1.57	50	< 0.4
" 47	0.79	6.25	6.25	1.57	1.57	3.13	50	< 0.4

Table 5-6

Compound		*Proteus mirabilis*	*Proteus morganii*	*Proteus vulgaris*	*Proteus rettgeri*
Control	Sodium Ampicillin	< 1.57	< 1.57	< 1.5	200
Control	Sodium Carbenicillin	0.8	0.4	0.8	> 200
Control	Sodium Sulbenicillin	0.79	< 0.4	< 0.4	> 200
Compound No. 16		1.56	1.56	0.8	6.25
" 30		3.13	3.13	3.13	12.5
" 36		< 0.4	< 0.4	< 0.4	12.5
" 37		0.79	0.79	< 0.4	25

- cont'd -

Table 5-6 (Cont'd)

Compound No. 38	< 0.4	< 0.4	< 0.4	12.5
" 39	< 0.4	< 0.4	< 0.4	6.25
" 40	< 0.4	0.79	< 0.4	6.25
" 45	< 0.4	0.79	< 0.4	6.25
" 46	< 0.4	< 0.4	< 0.4	3.13
" 47	< 0.4	< 0.4	< 0.4	0.79

Table 6-1

	Compound	*Staphylococcus aureus*									
		MS 8619	MS 8588	MS 8713	MS 8596	MS 8684	F-1	F-2	F-3	F-4	F-5
Control	Sodium Cephaloglycin	1.56	3.13	3.13	1.56	1.56	3.13	1.56	1.56	3.13	25
Control	Sodium Cephalothin	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	1.56
Control	Sodium Cephazolin	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	0.78	< 0.4	< 0.4	< 0.4	0.78
Control	Cephalorizine	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	0.78
Compound No. 60		0.78	1.56	0.78	0.78	1.56	3.13	0.78	1.56	1.56	50
" 61		1.56	1.56	1.56	1.56	1.56	3.13	1.56	1.56	3.13	50
" 62		0.78	1.56	1.56	0.78	1.56	3.13	0.78	1.56	1.56	12.5

- cont'd -

Table 6-1 (Cont'd)

Compound No. 63	0.78	1.56	1.56	1.56	1.56	3.13	0.78	1.56	1.56	12.5
" 68	0.78	1.56	3.13	1.56	1.56	1.56	1.56	0.78	6.25	0.78
" 69	0.78	1.56	1.56	1.56	1.56	3.13	1.56	0.78	3.13	0.78

Table 6-2

	Compound	*Escherichia coli*								
		GN 3481	GN 3435	GN 3452	GN 3465	GN 3611	K-1	K-2	K-3	K-4
Control	Sodium Cephaloglycin	3.13	1.56	3.13	12.5	25	1.56	1.56	25	12.5
Control	Sodium Cephalothin	12.5	6.25	12.5	25	50	6.25	6.25	100	25
Control	Sodium Cephazolin	1.56	1.56	1.56	6.25	25	1.56	1.56	>200	3.13
Control	Cephalorizine	3.13	3.13	3.13	50	100	3.13	3.13	200	6.25
Compound No. 60		6.25	6.25	12.5	100	>200	6.25	12.5	200	25
" 61		3.13	3.13	6.25	50	200	3.13	6.25	100	6.25
" 62		6.25	6.25	6.25	25	200	6.25	12.5	200	12.5
" 63		3.13	3.13	12.5	25	100	3.13	6.25	50	6.25

Table 6-3

Compound		*Pseudomonas aeruginosa*									
		GN 1035	GN 376	GN 82	GN 221	GN 1091	GN 2565	GN 2987	GN 163	GN 244	GN 383
Control	Sodium Cephaloglycin	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
Control	Sodium Cephalothin	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
Control	Sodium Cephazolin	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
Control	Cephalorizine	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200
Compound No. 60		200	50	50	12.5	50	100	50	50	50	50
" 61		100	12.5	25	6.25	25	50	25	25	25	12.5
" 62		200	100	100	50	100	100	50	50	100	100

- cont'd -

Table 6-3 (Cont'd)

Compound No. 63	100	50	50	25	50	50	25	25	50	25
" 68	50	12.5	6.25	3.13	12.5	50	12.5	12.5	25	12.5
" 69	50	12.5	12.5	6.25	12.5	50	12.5	12.5	25	25

Table 6-4

Compound		*Pseudomonas aeruginosa*				*Klebsiella pneumoniae*		
		S-1	S-2	S-3	S-4	GN 4117	GN 4081	GN 917
Control	Sodium Cephaloglycin	> 200	> 200	> 200	> 200	3.13	3.13	1.56
Control	Sodium Cephalothin	> 200	> 200	> 200	> 200	6.25	12.5	3.13
Control	Sodium Cephazolin	> 200	> 200	> 200	> 200	3.13	3.13	1.56
Control	Cephalorizine	> 200	> 200	> 200	> 200	12.5	12.5	3.13
Compound No. 60		200	100	100	100	25	25	6.25
" 61		50	50	50	50	12.5	12.5	6.25
" 62		200	200	200	200	25	12.5	6.25

- cont'd -

Table 6-4 (Cont'd)

Compound No. 63	100	100	100	100	6.25	6.25	3.13
" 68	25	25	25	25	-	-	1.56
" 69	25	25	50	50	-	-	0.78

Table 6-5

Compound	*Proteus*			
	mirabilis	*morganii*	*vulgaris*	*rettgeri*
Sodium Cephaloglycin	3.13	1.56	50	50
Compound No. 60	3.13	3.13	1.56	6.25
" 61	1.56	1.56	0.8	3.13
" 62	6.25	3.13	3.13	6.25
" 63	3.13	3.13	1.56	3.13

(3) Resistant activity against β-lactamase, *Pseudomonas aeruginosa* GN 238:

The resistant activity of each compound against β-lactamase was measured in the manner described below.

β-Lactamase was prepared from Psuedomonas aeruginosa GN 238. This microorganism was cultured in 100 ml of a medium containing 2 g of yeast extract. 10 g of polypeptone, 2 g of glucose, 7 g of disodium hydrogen phosphate, 2 g of potassium dihydrogen phosphate, 1.2 g of ammonium sulfate and 0.4 g of magnesium sulfate, per liter, in a 500-ml Erlenmeyer flask for 6 hrs. at 37°C with shaking. The resulting cells were collected by centrifugation (5,000 r.p.m. × 10 min.), washed three times with 0.1 M phosphate buffer (pH 7.0). Subsequently, the cells were subjected to sonication (20 KH_{z}, 20 min.) and then centrifuged at 15,000 r.p.m. for 60 min. By using the supernatant of enzyme fluid, the resistance of each compound against β-lactamase was determined by the iodometric assay method. The results obtained were as set forth in Table 7. Each numeral shown in Table 7 is a relative activity value calculated by assuming as 100 the activity of the control Potassium Penicillin G.

Table 7

Comparison of resistant activity against β-lactamase

Compound		Relative activity (%)
Control	Potassium Penicillin G	100
	Sodium Ampicillin	115
	Sodium Carbenicillin	116
	Sodium Sulbenicillin	50
Compound No. 30		3
" 36		14
" 37		15
" 38		15
" 39		15
" 40		15
" 45		16
" 46		12
" 47		1

From Tables 3 to 6, it is understood that the compounds of the present invention have a broader antibacterial spectrum and more excellent antibacterial activity against not only *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Proteus* species but also many drug-resistant bacteria than the control ampicillin and cephaloglycin, i.e. compounds having an amino group at the α-position of the acyl group. It is also understood from Table 7 that the compounds of the present invention are far higher in resistance to β-lactamase than the control drugs.

As is clear from the above results, the compounds represented by the formula (Ie), among the compounds of the present invention, show prominent effects, and particularly preferable compounds are those of the formula (Ie), in which A represents a hydrogen atom, or an unsubstituted or substituted alkyl, alkenyl, aryl or aralkyl group; and R^8 and R^9 represent individually a hydrogen atom or an alkyl group.

The present penicillins and cephalosporins have generally low toxicity. For example, 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid and 6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1-piperazinocarbonylamino)phenylacetamido]penicillanic acid have LD_{50} (i.v. in mouse having a weight of 19±1 g) greater than 5 g/kg.

The compounds of formula (I) of the present invention may be administered not only in the form of free acids but also in the form of non-toxic salts or physiologically acceptable esters. Further, the compounds, which are in the form of physiologically unacceptable esters, are ordinarily put into uses after bringing them to the form of free acids or non-toxic salts by removing the ester-forming group according to a conventional procedure known in this technical field.

The compounds of the present invention can be administered to humans and animals after formulating them into a physiological form such as tablet, capsule, syrup, injection or the like which is usually adopted in the case of penicillin and cephalosporin type drugs.

Procedures for producing the compounds of the present invention are shown below with reference to examples.

Example 1.

(1) To a mixture comprising 2.5 g of 1-acetyl-3-oxo-piperazine, 3.45 g of triethylamine and 20 ml of anhydrous dioxane was added a solution of 3.71 g of trimethylchlorosilane in 10 ml of anhydrous dioxane. The resulting mixture was refluxed for 17 hours and cooled to deposit triethylamine hydrochloride, which was then removed by filtration. The filtrate was dropped at −40° to −30°C into a solution of 1.8 g of phosgene in 30 ml of anhydrous methylene chloride. After the dropping, the resulting mixture was elevated in temperature, and reacted at room temperature for 30 minutes. Subsequently, the excess phosgene and the solvent were removed by distillation under reduced pressure to obtain 3.5 g of pale brown, oily 4-acetyl-2-oxo-1-piperazinocarbonyl chloride.

IR (film) cm^{-1}: $\nu_{C=O}$ 1790, 1710, 1640

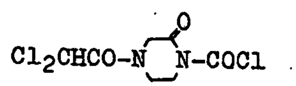
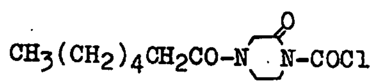
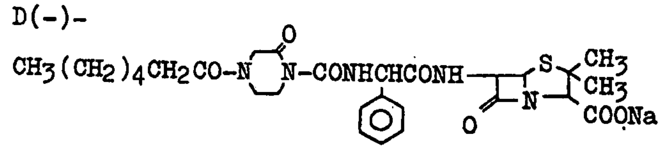
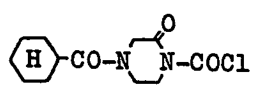
(2) A suspension of 1.0 g. of 6-[D(−)-α-aminophenylacetamido]penicillanic acid in 20 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension was dropped a solution of 900 mg of the aforesaid 4-acetyl-2-oxo-1-piperazinocarbonyl chloride in 5 ml of tetrahydrofuran at said temperature over a period of 30 minutes. During this period, the pH of the suspension was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the temperature of resulting mixture was elevated to 5° to 10°C, and the mixture was reacted at said temperature for 1 hour while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the tetrahydrofuran was removed by reduced pressure distillation, and the residue was dissolved in a mixed solvent comprising 30 ml of ethyl acetate and 10 ml of water. The resulting solution was adjusted to a pH of 1.5 to 2 by addition of dilute hydrochloric acid with ice-cooling, and then the organic layer was separated off. The aqueous layer was re-extracted with 20 ml of ethyl acetate, and the resulting organic layer was combined with the aforesaid organic layer. The combined organic layer was washed with water, dried over anhydrous magnesium sulfate, and then ice-cooled. Into this organic layer was dropped a solution of 470 mg of a sodium salt of 2-ethylhexanoic acid in 20 ml of ethyl acetate to deposit white crystals. The deposited crystals were collected by filtration, washed with ethyl acetate and then dried to obtain 1.4 g of a sodium salt of 6-[D(−)-α-(4-acetyl-2-oxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 205°C (decomp.), yield 94%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760 (lactam), 1600—1700 (—COO$^{\ominus}$, —CON<)
NMR: [$(CD_3)_2SO+D_2O$] τ values: 2.73 (5H), 4.35 (1H), 4.75 (2H), 5.75 (1H), 5.84 (2H), 6.42 (4H), 8.03 (3H), 8.52 (3H), 8.64 (3H)

The above-mentioned operation was repeated, except that the 4-acetyl-2-oxo-1-

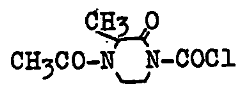
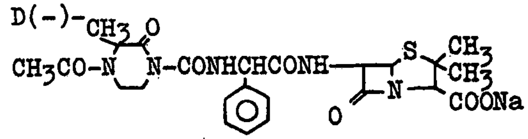
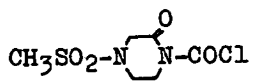
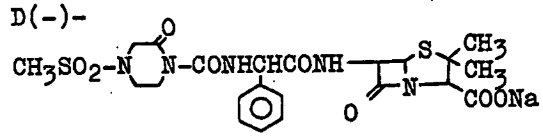
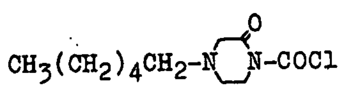
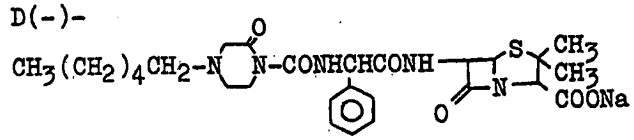
piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 8, to obtain the respective objective compounds as shown in Table 8. The structure of each objective compound was confirmed by IR and NMR.

Table 8

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 203 - 205°C, yield 73 %
	D(-)-  m.p. (decomp.) 202°C, yield 85.5 %
	D(-)-  m.p. (decomp.) 203 - 205°C, yield 87.7 %

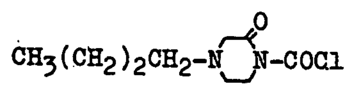
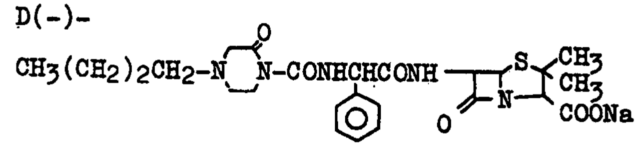
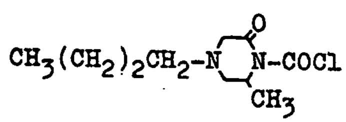
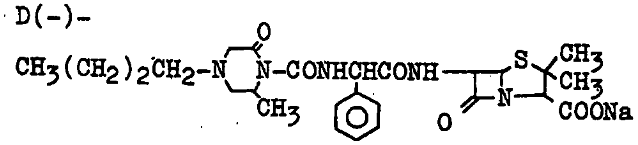
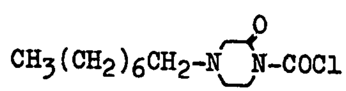
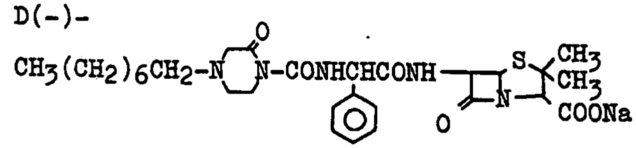
- cont'd -

Table 8 (Cont'd)

	D(-)-  m.p. (decomp.) 199 - 200°C, yield 95 %
	D(-)-  m.p. (decomp.) 199°C, yield 80 %
	D(-)-  m.p. (decomp.) 171 - 174°C, yield 74 %

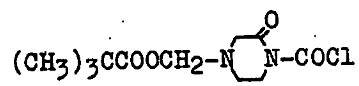
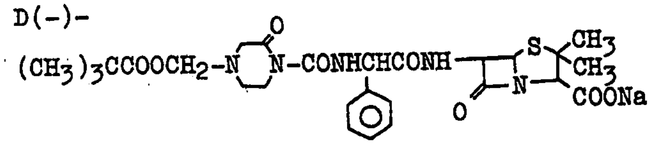
- cont'd -

Table 8 (Cont'd)

	D(-)-  m.p. (decomp.) 158 - 161°C, yield 69 %
	D(-)-  m.p. (decomp.) 188 - 190°C, yield 81 %
	D(-)-  m.p. (decomp.) 132 - 134°C, yield 63 %

- cont'd -

Table 8 (Cont'd)

	D(-)-  m.p. (decomp.) 218°C, yield 80 %

Example 2.

(1) Into a solution of 1.74 g of a sodium salt of D(−)-α-aminophenylacetic acid in 30 ml of tetrahydrofuran containing 20% by volume of water which had been cooled to 0°C, a solution of 2.5 g of 4-acetyl-2-oxo-1-piperazinocarbonyl chloride in 5 ml of tetrahydrofuran was dropped at said temperature over a period of 30 minutes. During this period, the pH of the reaction solution was maintained at 1.0 to 12.0 by gradual addition of a 10% aqueous sodium hydroxide solution. Subsequently, the temperature of the resulting mixed solution was elevated to 5° to 10°C, and the solution was reacted at room temperature for 2 hours while maintaining the pH thereof at 10.0 to 11.0 by addition of a 10% aqueous sodium hydroxide solution. After the reaction, the tetrahydrofuran was removed by reduced pressure distillation. The residue was dissolved in a mixed solvent comprising 20 ml of water and 50 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.0 to 1.5 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, washed with water and then dried over anhydrous magnesium sulfate. To this organic layer, a solution of 1.66 g of a sodium salt of 2-ethylhexanoic acid in 20 ml of ethyl acetate was added to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with ethyl acetate and then dried to obtain 1.89 g of a sodium salt of D(−)-α-(4-acetyl-2-oxo-1-piperazinocarbonylamino)phenylacetic acid, m.p. 115°C (decomp.), yield 52%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1690, 1650—1600

(2) To a suspension in 15 ml of anhydrous acetone of 833 mg of the above-mentioned sodium salt of D(−)-α-(4-acetyl-2-oxo-1-piperazinocarbonylamino)phenylacetic acid was added 10 mg of N-methylmorpholine. The resulting mixture was colled to −20° to −15°C, and a solution of 286 mg of ethyl chlorocarbonate in 5 ml of anhydrous acetone was dropped into said mixture over a period of 5 minutes. Sub-

sequently, the mixture was stirred at said temperature for 60 minutes. Into the thus treated mixture, a solution of 646 mg of a triethylamine salt of 6-aminopenicillanic acid in 30 ml of anhydrous methylene chloride was dropped at −40° to −30°C over a period of 10 minutes. Thereafter, the mixture was reacted with stirring at −30° to −20°C for 60 minutes, at −20° to −10°C for 30 minutes, and at −10° to 0°C for 30 minutes. After the reaction, the organic solvent was removed by reduced pressure distillation. The residue was dissolved in a mixed solvent comprising 50 ml of ethyl acetate and 20 ml of water, and the resulting solution was adjusted to a pH of 1.5 to 2.0 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, sufficiently washed with water and then dried over anhydrous magnesium sulfate, and the ethyl acetate was removed by reduced pressure distillation. The residue was dissolved in 50 ml of acetone, and the resulting solution was mixed with a solution of 340 mg of a sodium salt of 2-ethylhexanoic acid in 20 ml of acetone with ice-cooling to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with acetone and then dried to obtain 1.16 g of a sodium salt of 6 - [D(−) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - penicillanic acid, m.p. 205°C (decomp.), yield 94%.

Example 3.

(1) To a mixture comprising 1.0 g of 1-palmitoyl-3-oxo-piperazine, 0.6 g of triethylamine and 20 ml of anhydrous dioxane was added a solution of 0.65 g of trimethylchlorosilane in 10 ml of anhydrous dioxane. The resulting mixture was refluxed for 16 hours and cooled to deposit triethylamine hydrochloride, which was then removed by filtration. The filtrate was dropped at −40° to −30°C into a solution of 0.6 g of phosgene in 30 ml of anhydrous methylene chloride. After the dropping, the temperature of the resulting mixture was elevated and the mixture was reacted at room temperature for 30 minutes. Subsequently, the excess phosgene and the solvent were removed by reduced pressure distillation to obtain 1.1 g of pale yellow, oily 4-palmitoyl-2-oxo-1-piperazinocarbonyl chloride.

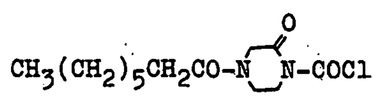
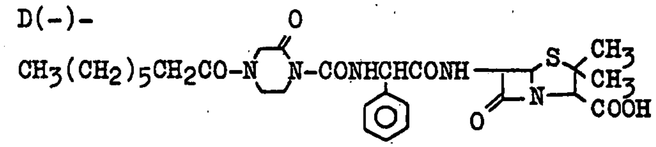
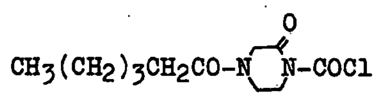
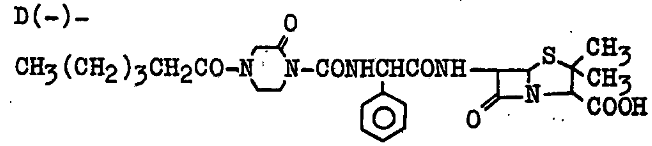
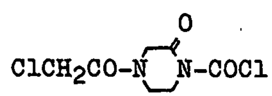
IR (film) cm^{-1}: $\nu_{C=O}$ 1740, 1660, 1640

(2) A suspension of 1.0 g of 6-[D(−)-α-aminophenylacetamido]penicillanic acid in 20 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension, a solution of 1.27 g of the aforesaid 4-palmitoyl-2-oxo-1-piperazinocarbonyl chloride in 5 ml of tetrahydrofuran was dropped at said temperature over a period of 30 minutes. During this period, the pH of the suspension was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the temperature of the resulting mixture was elevated to 5° to 10°C, and the mixture was reacted at said temperature for 1 hour while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the tetrahydrofuran was removed by reduced pressure distillation, and the residue was dissolved in a mixed solvent comprising 30 ml of ethyl acetate and 10 ml of water. The resulting solution was adjusted to a pH of 1.0 to 2.0 by addition of dilute hydrochloric acid with ice-cooling, and then the organic layer was separated off. The aqueous layer was re-extracted with 20 ml of ethyl acetate, and the resulting organic layer was combined with the aforesaid organic layer. The combined organic layer was washed with water, and dried over anhydrous magnesium sulfate. This organic layer was concentrated under reduced pressure to remove the solvent, and the concentrate was charged into 10 ml of diisopropyl ether to deposit crystals. Thereafter, the crystals were collected by filtration to obtain 1.65 g of white crystals of 6-[D(−)-α-(4-palmitoyl-2-oxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 121—123°C (decomp.), yield 80%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1770 (lactam), 1730 (—COOH), 1660—1630 (—CON<).

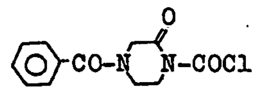
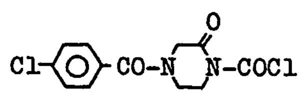
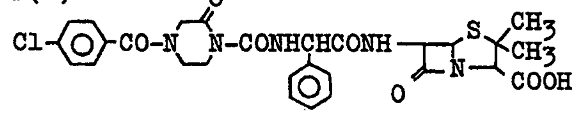
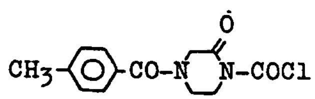
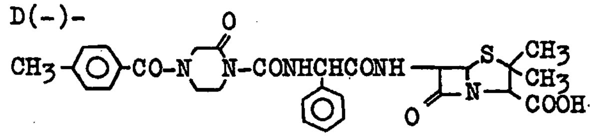
The above-mentioned operation was repeated, except that the 4-palmitoyl-2-oxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 9, to obtain respective objective compounds as shown in Table 9. The structure of each objective compound was confirmed by IR and NMR.

Table 9

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 151 - 153°C, yield 82 %
	D(-)-  m.p. (decomp.) 157 - 158°C, yield 83.3 %
	D(-)-  m.p. (decomp.) 215°C, yield 82.6 %

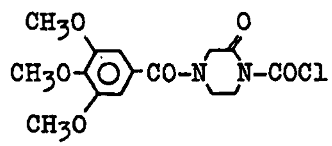
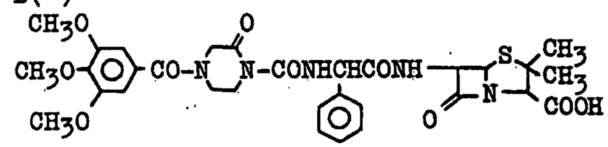
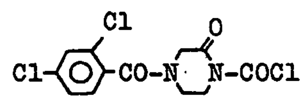
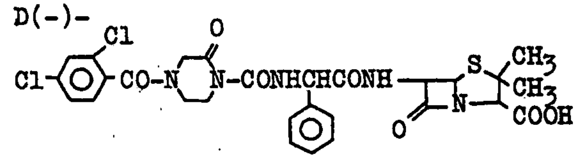
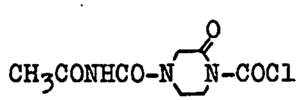
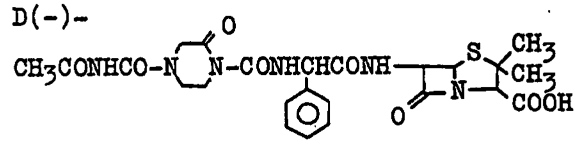
- cont'd -

Table 9 (Cont'd)

	 m.p. (decomp.) 120 - 124°C, yield 80 %
	D(-)-  m.p. (decomp.) 120 - 123°C, yield 91 %
	D(-)-  m.p. (decomp.) 105 - 108°C, yield 88.6 %

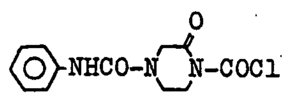
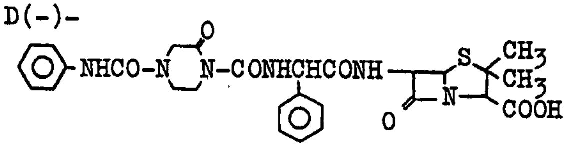
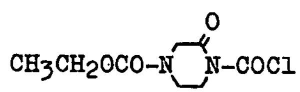
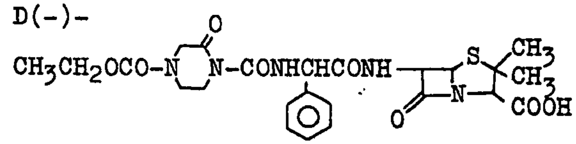
- cont'd -

Table 9 (Cont'd)

	D(-)-  m.p. (decomp.) 120 - 124°C, yield 86.1 %
	D(-)-  m.p. (decomp.) 130 - 133°C, yield 92 %
	D(-)-  m.p. (decomp.) 172 - 176°C, yield 79.2 %

- cont'd -

Table 9 (Cont'd)

	D(-)-  m.p. (decomp.) 168 - 170°C, yield 83.3 %
	D(-)-  m.p. (decomp.) 86°C, yield 91 %

Example 4.

(1) To a solution of 6.4 g of 1-formyl-3-oxo-piperazine in 10 ml of anhydrous dimethylformamide was added 2.7 g of a sodium hydride (purity 53%) with ice-cooling and the resulting mixture was reacted at room temperature for 1 hour. Subsequently, the mixture was incorporated with 7.1 g of methyl iodide and reacted for 10 hours. After the reaction, the dimethylformamide was removed by reduced pressure distillation to obtain 1-formyl-4-methyl-3-oxo-piperazine. This piperazine was dissolved in 70 ml of a 50% aqueous acetone solution containing 2.2 g of sodium hydroxide, and the resulting solution was reacted at room temperature for 3 hours. Thereafter, the solvent was removed by distillation under reduced pressure, and the residue was charged into acetone to deposit insolubles. The insolubles were separated by filtration, and the acetone was removed from the filtrate by distillation under reduced pressure. Subsequently, the residue was subjected to reduced pressure distillation to obtain 5.2 g of 1-methyl-2-oxo-piperazine, b.p. 104°C/4 mmHg, yield 91%.

(2) Into a solution of 1.9 g of phosgene in 20 ml of anhydrous dioxane was dropped at 10°C 20 ml of an anhydrous dioxane solution containing 2.0 g of 1-methyl-2-oxo-piperazine and 1.95 g of triethylamine, upon which reaction took place to deposit white crystals of triethylamine hydrochloride. The deposited crystals were removed by filtration, and the filtrate was concentrated to dryness to obtain 3.0 g of pale yellow, oily 4-methyl-3-oxo-1-piperazinocarbonyl chloride.

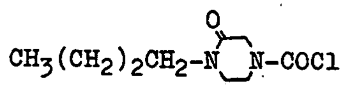
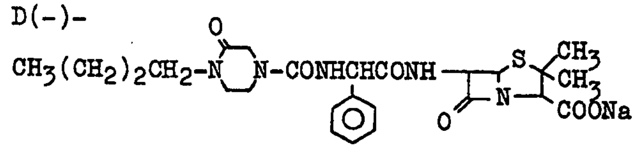
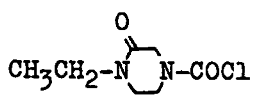
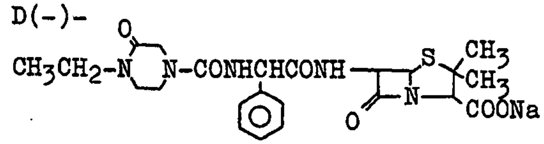
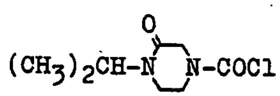
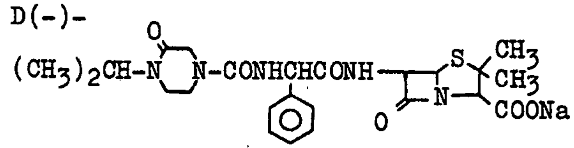
IR (film) cm^{-1}: $\nu_{C=O}$1710, 1630

(3) A suspension of 4.0 g of 6-[D(−)-α-aminophenylacetamido]penicillanic acid in 40 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension, 10 ml of a tetrahydrofuran solution containing 2.2 g of the aforesaid 4-methyl-3-oxo-1-piperazinocarbonyl chloride was dropped. During this period, the pH of the suspension was maintained at 7.5 to 8.5 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at said temperature for 30 minutes, and the temperature thereof was elevated to 10° to 15°C, after which the mixture was further reacted at said temperature for 90 minutes while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 30 ml of water. The resulting solution was washed with ethyl acetate, and then the aqueous layer was separated off. This aqueous layer was ice-cooled and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, washed several times with a small amount of water, dried, and then dissolved in 100 ml of acetone. To the resulting solution was added 1.9 g of a sodium salt of 2-ethylhexanoic acid with ice-cooling to deposit white crystals, which were then collected by filtration to obtain 5.4 g of a sodium salt of 6-[D(−)-α-(4-methyl-3-oxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 195°C (decomp.), yield 92%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760 (lactam), 1600—1660 (—CON<, —$COO^{\ominus}$)
NMR [$(CD_3)_2SO+D_2O$] τ values: 2.62 (5H), 4.48 (1H), 4.56 (2H), 5.97 (3H), 6.63—6.39 (4H), 7.13 (3H), 8.46 (3H), 8.55 (3H)

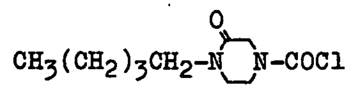
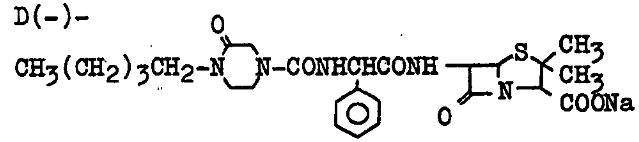
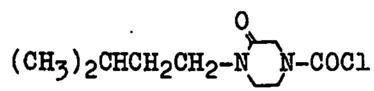
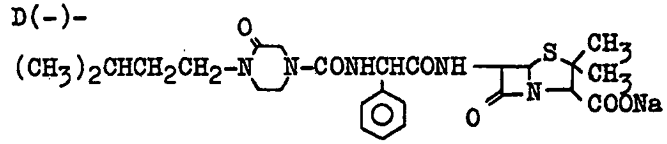
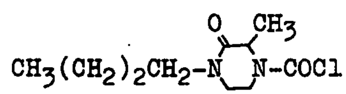
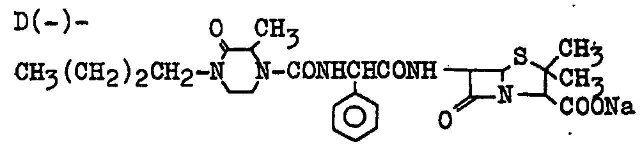
The above-mentioned operation was repeated, except that the 4-methyl-3-oxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 10, to obtain respective objective compounds as shown in Table 10. The structure of each objective compound was confirmed by IR and NMR.

Table 10

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 206 - 207°C, yield 90 %
	D(-)-  m.p. (decomp.) 207°C, yield 96 %
	D(-)-  m.p. (decomp.) 208°C, yield 87 %

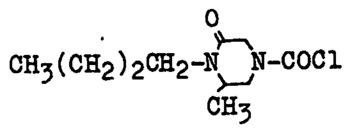
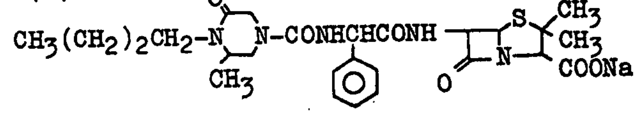
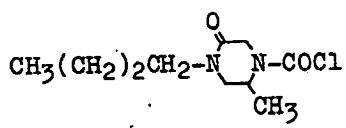
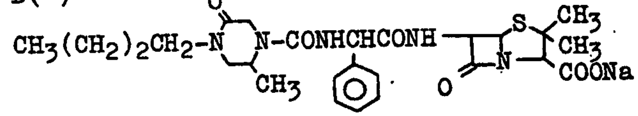
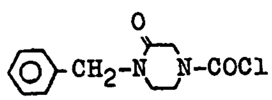
- cont'd -

Table 10 (Cont'd)

	D(-)-  m.p. (decomp.) 200°C, yield 96 %
	D(-)-  m.p. (decomp.) 185°C, yield 90 %
	D(-)-  m.p. (decomp.) 193 - 197°C, yield 74 %

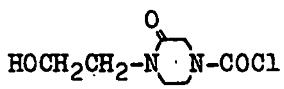
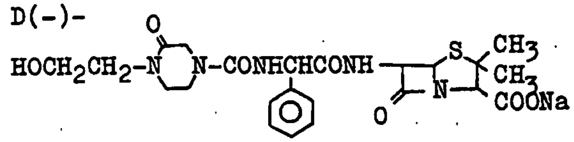
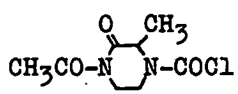
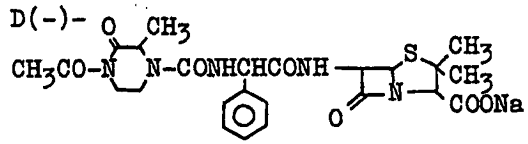
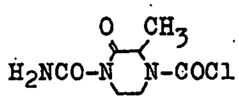
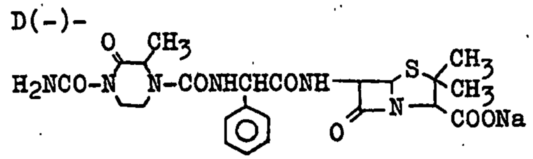
- cont'd -

Table 10 (Cont'd)

	D(-)-  m.p. (decomp.) 199 - 202°C, yield 93 %
	D(-)-  m.p. (decomp.) 191 - 194°C, yield 88 %
	D(-)-  m.p. (decomp.) 100 - 105°C, yield 90 %

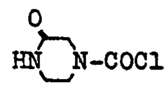
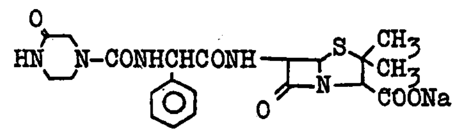
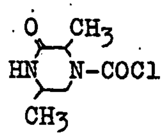
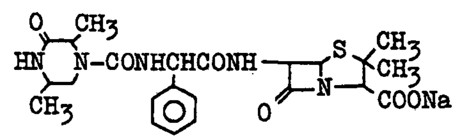
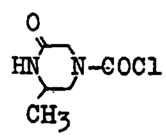
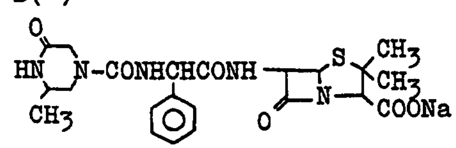
- cont'd -

Table 10 (Cont'd)

	D(-)-  m.p. (decomp.) 100 - 105°C, yield 67 %
	D(-)-  m.p. (decomp.) 202°C, yield 66 %
	D(-)-  m.p. (decomp.) 215°C, yield 65 %

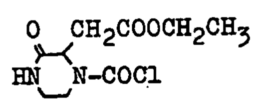
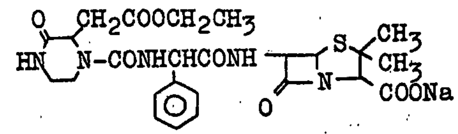
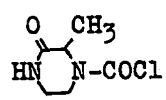
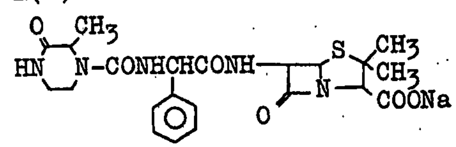
- cont'd -

Table 10 (Cont'd)

	 m.p. (decomp.) 213°C, yield 70 %
	D(-)-  m.p. (decomp.) 203 - 206°C, yield 82 %
	D(-)-  m.p. (decomp.) 216 - 218°C, yield 87 %

- cont'd -

Table 10 (Cont'd)

	D(-)-  m.p. (decomp.) 200°C, yield 98 %
	D(-)-  m.p. (decomp.) 208°C, yield 75 %

Example 5.

(1) A solution of 1.0 g of a sodium salt of D(−)-α-aminophenyl acetic acid in 20 ml of tetrahydrofuran containing 20% by volume of water was cooled to 0° to 5°C. To this solution was added 1.2 g of 2-methyl-3-oxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the solution was maintained at 11.0 to 12.0 by gradual addition of a 10% aqueous sodium hydroxide solution. The solution was reacted at said temperature for 1 hour, and the temperature thereof was elevated to 5° to 10°C, after which the mixture was further reacted at said temperature for 2 hours, while maintaining the pH thereof at 10.0 to 11.0 by addition of a 10% aqueous sodium hydroxide solution. After the reaction, tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in a mixed solvent comprising 20 ml of water and 50 ml of ethyl acetate. The resulting solution was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling, and then the organic layer was separated off. The aqueous layer was further extracted with 50 ml of ethyl acetate, and the resulting organic layer was combined with the aforesaid organic layer. The combined organic layer was washed with water and then dried over anhydrous magnesium sulfate. To this organic layer was added 0.9 g of a sodium salt

of 2-ethylhexanoic acid to deposit white crystals. The deposited crystals were collected by filtration and then dried to obtain 1.26 g of white crystals of a sodium salt of D(−) - α - (2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid, m.p. 215°C (decomp.), yield 70%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1650—1590

(2) To a suspension in 15 ml of anhydrous acetone of 1.0 g of the above-mentioned sodium salt of D(−)-α-(2-methyl-3-oxo-1-piperazinocarbonylamino)phenylacetic acid was added 10 mg of N-methylmorpholine. The resulting mixture was cooled to −20° to −15°C, and a solution of 380 mg of ethyl chlorocarbonate in 5 ml of anhydrous acetone was dropped into said mixture over a period of 5 minutes. Subsequently, the mixture was stirred at said temperature for 60 minutes, and then cooled to −40° to −30°C. Into the thus treated mixture was dropped a solution of 960 mg of a triethylamine salt of 6-aminopenicillanic acid in 10 ml of anhydrous methylene chloride over a period of 10 minutes. Thereafter, the mixture was reacted with stirring at −30° to −20°C for 60 minutes, at −20° to −10°C for 30 minutes, and at −10° to 0°C for 30 minutes. After the reaction, the organic solvent was removed by distillation under reduced pressure. The residue was dissolved in a mixed solvent comprising 20 ml of water and 50 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, sufficiently washed with water and then dried over anhydrous magnesium sulfate. To this organic layer was added 0.5 g of a sodium salt of 2-ethylhexanoic acid with ice-cooling to deposit white crystals. The deposited crystals were collected by filtration, and then dried to obtain 1.39 g of a sodium salt of 6-[D(−)-α-(2-methyl-3-oxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 208°C (decomp.), yield 90%.

In the same manner as above, 2.0 g of a sodium salt of 6 - [D(−) - α-(4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)propionamido]penicillanic acid, m.p. 195°C (decomp.), yield 86%, was obtained from 1.59 g of a sodium salt of D(−) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)propionic acid and 1.59 g of a triethylamine salt of 6-aminopenicillanic acid.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760 (lactam), 1680—1600 (—CON<, —COO$^{\ominus}$)

Example 6.

(1) Into a solution of 0.5 g of phosgene in 10 ml of anhydrous dioxane was dropped at 10°C 10 ml of anhydrous dioxane containing 0.56 g of 1-allyl-2-oxo-piperazine and 0.5 g of triethylamine, upon which reaction took place to deposit white crystals of triethylamine hydrochloride. Subsequently, the deposited crystals were collected by filtration, and the filtrate was concentrated to dryness to obtain 800 mg of pale yellow, oily 4-allyl-3-oxo-1-piperazinocarbonyl chloride.

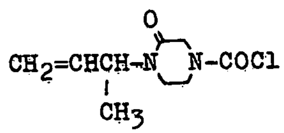
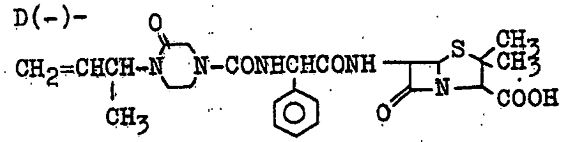
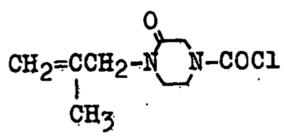
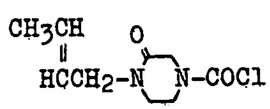
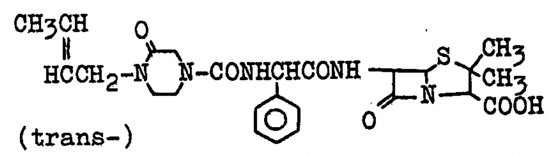
IR (film) cm^{-1}: $\nu_{C=O}$ 1720, 1640

(2) A suspension of 1.4 g of 6-[D(−)-α-aminophenylacetamido]penicillanic acid in tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension was dropped 10 ml of a tetrahydrofuran solution containing 800 mg of the aforesaid 4-allyl-3-oxo-1-piperazinocarbonyl chloride. During this period, the pH of the suspension was maintained at 7.5 to 8.5 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at said temperature for 30 minutes, and the temperature thereof was then elevated to 10° to 15°C, after which the mixture was further reacted at said temperature for 90 minutes while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water. The resulting solution was washed with ethyl acetate, and the aqueous layer was then separated off. This aqueous layer was ice-cooled and adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 1.8 g of 6-[D(−)-α-(4-allyl-3-oxo-1-piperazinocarbonylamino)-phenylacetamido]penicillanic acid, m.p. 92°C (decomp.), yield 90%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760 (lactam), 1720—1620 (—COOH, —CON<)

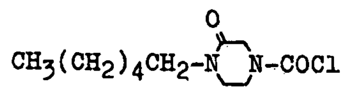
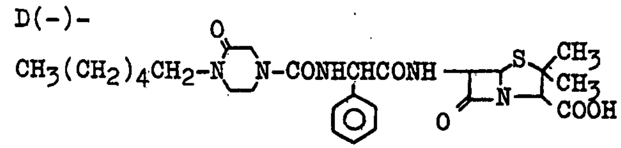
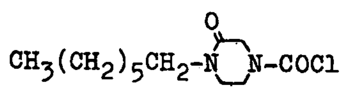
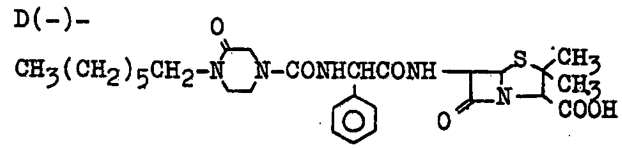
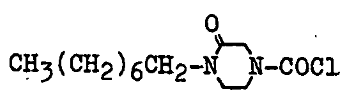
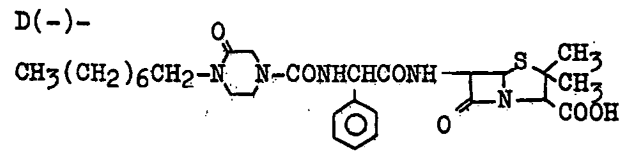
The above-mentioned operation was repeated, except that the 4-allyl-3-oxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 11, to obtain respective objective compounds as shown in Table 11. The structure of each objective compound was confirmed by IR and NMR.

Table 11

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 102°C, yield 80 %
	D(-)-  m.p. (decomp.) 90°C, yield 85 %
 (trans-)	D(-)-  (trans-) m.p. (decomp.) 95°C, yield 84 %

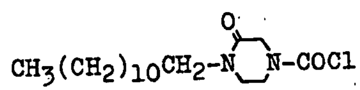
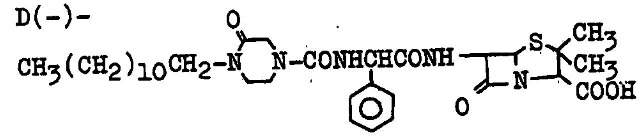
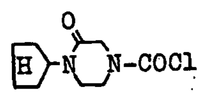
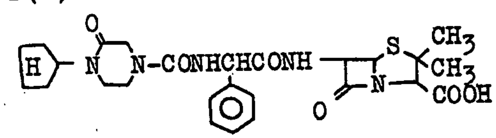
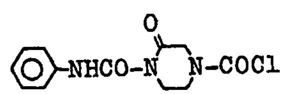
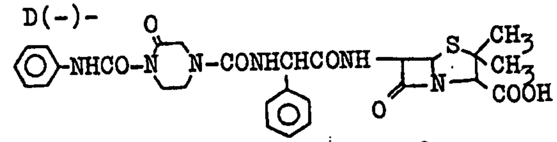
- cont'd -

Table 11 (Cont'd)

	 m.p. (decomp.) 128 - 130°C, yield 97 %
	 m.p. (decomp.) 120°C, yield 94 %
	 m.p. (decomp.) 110°C, yield 98 %

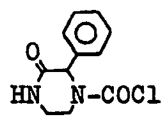
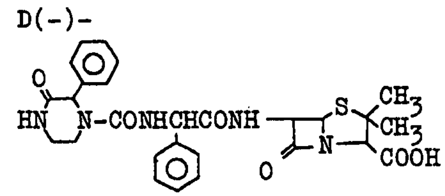
- cont'd -

Table 11 (Cont'd)

	D(-)-  m.p. (decomp.) 106°C, yield 96 %
	D(-)-  m.p. (decomp.) 134°C, yield 87 %
	D(-)-  m.p. (decomp.) 150 - 153°C, yield 76 %

- cont'd -

Table 11 (Cont'd)

	 m.p. (decomp.) 125 - 128°C, yield 79.5 %

Example 7.

Using 0.63 g of 6-[D(−)-α-aminophenylacetamido]penicillanic acid and 600 mg of a hydrochloride of 4-(N-morpholinomethyl)-3-oxo-1-piperazinocarbonyl chloride, the same operation as in Example 6 was repeated to obtain 0.63 g of 6-{D(−)-α-[4-(N-morpholinomethyl)-3-oxo-1-piperazinocarbonylamino]phenylacetamido}penicillanic acid, m.p. 85°C (decomp.), yield 60%.

IR (KBr) cm^{-1}: $\nu_{C=O}$: 1770 (lactam), 1600—1680 (—$COO^{\ominus}$, —CON<)

Example 8.

Using 5.0 g of a hydrochloride of pivaloyloxymethyl ester of 6-[D(−)-α-aminophenylacetamido]penicillanic acid and 1.94 g of 2-methyl-3-oxo-1-piperazinocarbonyl chloride, the same operation as in Example 6 was repeated to obtain 5.2 g of a pivaloyloxymethyl ester of 6-[D(−)-α-(2-methyl-3-oxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 140°C (decomp.), yield 80%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1740—1770 (lactam, ester) 1630—1670 (—CON<)

Example 9.

(1) Into a mixture comprising 8.0 g of 4-acetyl-2,5-dioxo-piperazine, 5.0 g of triethylamine and 100 ml of anhydrous tetrahydrofuran was dropped 6.0 g of trimethylchlorosilane with stirring at room temperature. After the dropping, the resulting mixture was reacted at said temperature for 2 hours to deposit triethylamine hydrochloride. The deposited hydrochloride was separated by filtration, and the filtrate was dropped at 0° to 5°C into 100 ml of an anhydrous tetrahydrofuran solution containing 10.0 g of phosgene. After completion of the dropping, the resulting mixture was stirred at 10°

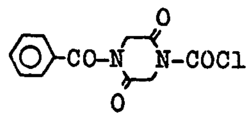
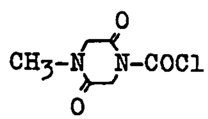
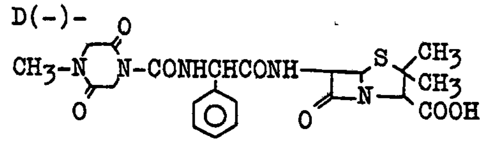
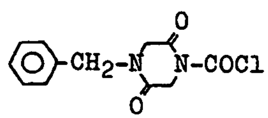
to 15°C for 3 hours to terminate the reaction. Subsequently, the tetrahydrofuran and the excess phosgene were removed by distillation under reduced pressure to obtain 11.0 g of oily 4-acetyl-2,5-dioxo-1-piperazinocarbonyl chloride.

(2) A suspension of 17.5 g of 6-[D(−)-α-aminophenylacetamido]penicillanic acid in 200 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethyl amine with stirring at 10° to 15°C to form a homogeneous solution. Into this solution was dropped a solution of 11.0 g of the aforesaid 4-acetyl-2,5-dioxo-1-piperazinocarbonyl chloride in 30 ml of tetrahydrofuran at 0°C over a period of 30 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the temperature of the resulting mixed solution was elevated to 5° to 10°C and the solution was further reacted for 1 hour while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After completion of the reaction, the tetrahydrofuran was removed by distillation under reduced pressure. To the residue was added 100 cc of N hydrochloric acid at 0° to 10°C. and the resulting mixture was stirred for 30 minutes to deposit white crystals. The deposited crystals were collected by filtration, and again suspended in water. The resulting aqueous suspension was adjusted to a pH of 8.0 by gradual addition of triethylamine at 5° to 10°C, and then freed from insolubles by filtration. The filtrate was adjusted to a pH of 1.5 by gradual addition of N-hydrochloric acid to deposit crystals. The deposited crystals were collected by filtration, washed with water and then dried to obtain 21.2 g of 6-[D(−)-α-(4-acetyl-2,5-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, b.p. 162—164°C (decomp.), yield 80%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1770 (lactam), 1730—1660 (—COOH, —CON<)
NMR ($(CD_3)_2CO$) τ values: 0.23 (1H), 2.65 (5H), 4.26 (1H), 4.33—4.63 (2H), 5.38 (4H), 5.68 (1H), 7.55 (3H), 8.47 (3H), 8.53 (3H)

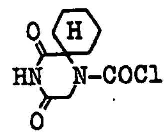
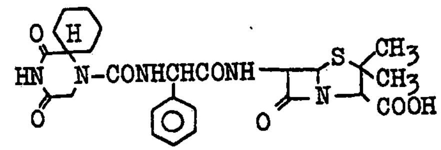
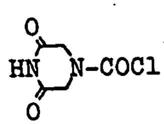
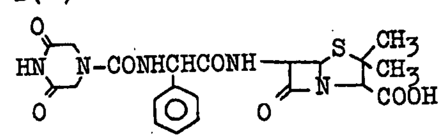
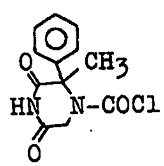
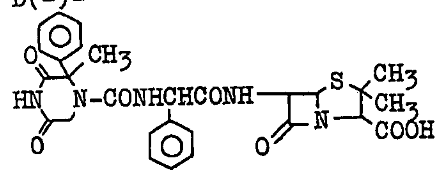
The above-mentioned operation was repeated, except that the 4-acetyl-2,5-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 12, to obtain respective objective compounds as shown in Table 12. The structure of each objective compound was confirmed by IR and NMR.

Table 12

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 88°C, yield 60 %
	D(-)-  m.p. (decomp.) 179 - 181°C, yield 83 %
	D(-)-  m.p. (decomp.) 88°C, yield 82 %

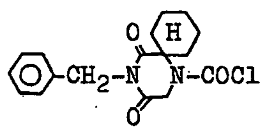
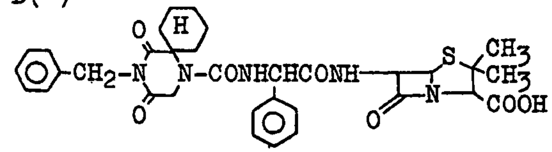
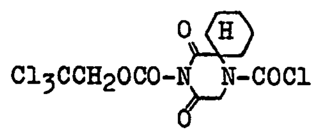
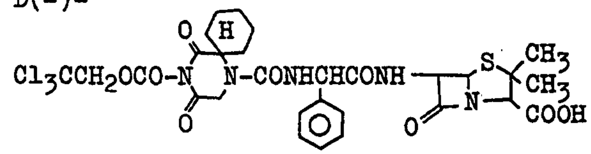
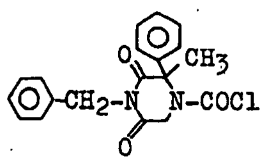
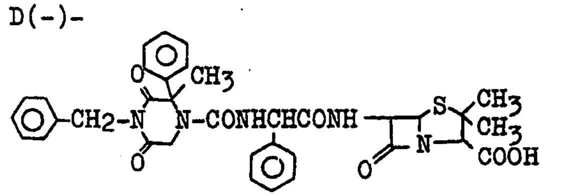
- cont'd -

Table 12 (Cont'd)

	D(-)-  m.p. 214 - 215°C, yield 89.6 %
	D(-)-  m.p. (decomp.) 176 - 181°C, yield 84.4 %
	D(-)-  m.p. (decomp.) 148 - 151°C, yield 92 %

- cont'd -

Table 12 (Cont'd)

	D(-)-  m.p. (decomp.) 95 - 100°C, yield 91 %
	D(-)-  m.p. (decomp.) 120 - 125°C, yield 92 %
	D(-)-  m.p. (decomp.) 147 - 149°C, yield 89 %

Example 10.

(1) A suspension of 8.0 g of D(−)-α-aminophenyl acetic acid in 80 ml of tetrahydrofuran was adjusted to a pH of 11.5 by gradual addition of a N sodium hydroxide solution with stirring to form a homogeneous solution. This solution was cooled to 0°C, and 15 ml of a tetrahydrofuran solution containing 11 g of 4-acetyl-2,5-dioxo-1-piperazinocarbonyl chloride was dropped at said temperature into said solution over a period of 30 minutes. During this period, the pH of the reaction solution was maintained at 10.5 to 11.0 by gradual addition of a N sodium hydroxide solution. Subsequently, the temperature of the resulting mixed solution was elevated to 5° to 10°C, and the mixture was further reacted for 1 hour, upon which D(−)-α-aminophenylacetic acid deposited. After completion of the reaction, the deposited acid was separated by filtration, and the filtrate was concentrated under reduced pressure to remove tetrahydrofuran. The residue was dissolved in a mixed solvent comprising 10 ml of water and 80 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.0 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, dried over anhydrous magnesium sulfate, and then charged into 100 ml of an ethyl acetate solution containing 8.3 g of sodium 2-ethylhexanoate to deposit crystals. The deposited crystals were collected by filtration, washed with acetone, and then dried over P_2O_5 to obtain 7.9 g of a sodium salt of D(−)-α-(4-acetyl-2,5-dioxo-1-piperazinocarbonylamino)phenylacetic acid, m.p. 104°C (decomp.), yield 42%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1690—1650, 1600—1590

(2) To a suspension in 25 ml of anhydrous acetone of 1.75 g of the aforesaid sodium salt of D(−)-α-(4-acetyl-2,5-dioxo-1-piperazinocarbonylamino)phenylacetic acid was added 20 mg of N-methylmorpholine, and the resulting mixture was cooled to −20° to −15°C. Into this mixture was dropped a solution of 0.57 g of ethyl chlorocarbonate in 5 ml of anhydrous acetone over a period of 5 minutes, and the mixture was stirred at said temperature for 60 minutes. Subsequently, a solution of 1.29 g of a triethylamine salt of 6-aminopenicillanic acid in 30 ml of anhydrous methylenechloride was dropped into said mixture at −40° to −30°C over a period of 10 minutes. The temperature of the resulting mixture was elevated from −30°C to 0°C, and the mixture was then reacted at said temperature for about 2 hours. After the reaction, the solvent was removed by distillation under reduced pressure. The residue was charged into 30 ml of water, and the resulting mixture was freed from insolubles by filtration with ice-cooling. The filtrate was adjusted to a pH of 1.5 to 2.0 by addition of dilute hydrochloric acid to deposit crystals. The deposited crystals were collected by filtration, sufficiently washed with water, and then dried to obtain 2.34 g of 6-[D(−)-α-(4-acetyl-2,5-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 162—164°C (decomp.), yield 90%.

In the same manner as above, 530 mg of 6-[D(−)-α-(4-benzyl-2,2-pentamethylene-3,5-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 95—100°C, yield 82.68%, was obtained from 450 mg of D(−)-α-(4-benzyl-2,2-pentamethylene-3,5-dioxo-1-piperazinocarbonylamino)phenylacetic acid and 320 mg of a triethylamine salt of 6-amino-penicillanic acid.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1770 (lactam), 1700—1660 (—COOH, —CON<)

Example 11.

(1) Into a mixture comprising 8 g of a diethyl ester of oxalic acid and 8 ml of ethanol was dropped at room temperature 4.4 g of N-ethyl ethylenediamine. The resulting mixture was allowed to react for 3 hours, and then heated to remove the ethanol. Subsequently, the residue was recrystallized from 10 ml of dioxane to obtain 5.4 g of 1-ethyl-2,3-dioxo-piperazine, m.p. 124°C, yield 76.0%.

(2) To a suspension of 0.71 g of the above-mentioned 1-ethyl-2,3-dioxo-piperazine in 15 ml of anhydrous dioxane were added with stirring 0.70 g of trimethylsilyl chloride and 0.83 ml of triethylamine. The resulting mixture was stirred at room temperature for 20 hours to deposit triethylamine hydrochloride. This hydrochloride was separated by filtration, and the filtrate was dropped at 5° to 10°C into a solution of 0.70 g of phosgene in 10 ml of anhydrous tetrahydrofuran. Subsequently, the resulting mixture was reacted at 5° to 10°C for 30 minutes and at room temperature for 2 hours, and then the solvent was removed by distillation under reduced pressure to obtain 1.0 g of pale yellow crystals of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride.

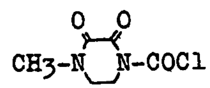
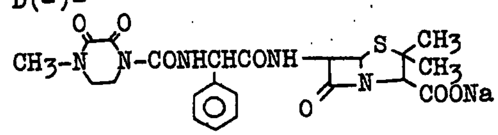
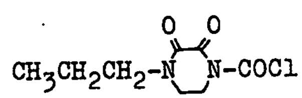
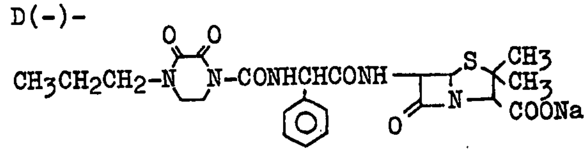
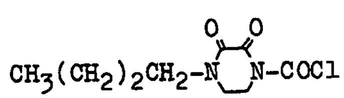
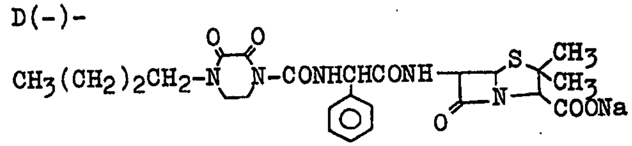
IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780, 1660

(3) A suspension of 1.75 g of 6-[D(−)-α-aminophenylacetamido]penicillanic acid in 50 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This solution was cooled to 0° to 5°C, and then 7 ml of an anhydrous tetrahydrofuran solution containing 1.0 g of the aforesaid 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride was dropped into the solution. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. The resulting mixed solution was reacted at said temperature for 30 minutes and then at 5° to 10°C for 1 hour, while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. To the aqueous layer was again added 50 ml of ethyl acetate, and the resulting mixture was adjusted to a pH of 1.5 by gradual addition of dilute hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, sufficiently washed with water, and then dried over anhydrous magnesium sulfate. Into the thus treated layer was dropped 10 ml of an ethyl acetate solution containing 0.83 g of sodium 2-ethyl-hexanoate to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with ethyl acetate, washed with diethyl ether, and then dried to obtain 2.4 g of a sodium salt of 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 183—185°C (decomp.), yield 89%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1765 (lactam), 1720—1670 (—CON<), 1600 ($—COO^{\ominus}$)
NMR ($(CD_3)_2SO+D_2O$) τ values: 2.62 (5H), 4.31 (1H), 4.50 (1H), 4.70 (1H), 6.05 (1H), 6.35—6.65 (6H), 8.49 (3H), 8.60 (3H), 8.91 (3H)

The above-mentioned operation was repeated, except that the 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 13, to obtain respective objective compounds as shown in Table 13. The structure of each objective compound was confirmed by IR and NMR.

Table 13

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 170°C, yield 84 %
	D(-)-  m.p. (decomp.) 170°C, yield 86 %
	D(-)-  m.p. (decomp.) 190°C, yield 87 %

- cont'd -

Table 13 (Cont'd)

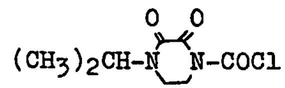
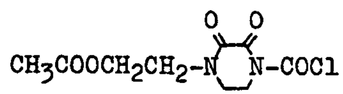
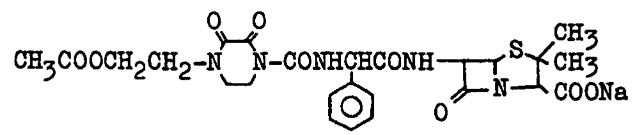
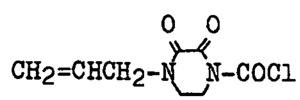
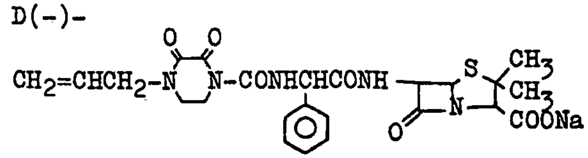
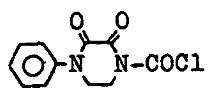
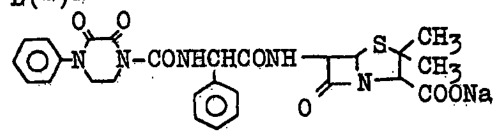
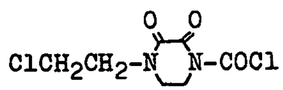
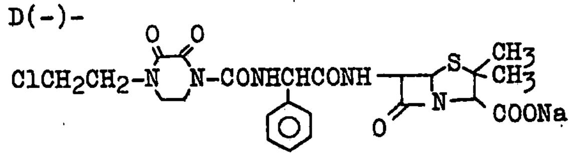
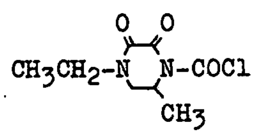
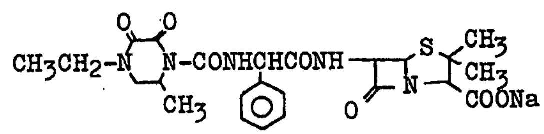
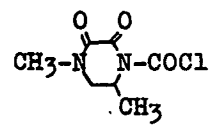
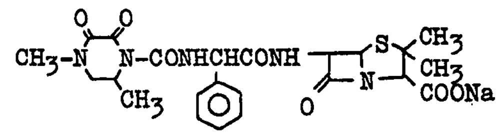
	D(-)-  m.p. (decomp.) 186°C, yield 85 %
	D(-)-  m.p. (decomp.) 175°C, yield 79 %
	D(-)-  m.p. (decomp.) 198 - 200°C, yield 75 %

Table 13 (Cont'd)

	D(-)-  m.p. (decomp.) 185 - 187°C, yield 88 %
	D(-)-  m.p. (decomp.) 210°C, yield 83 %
	D(-)-  m.p. (decomp.) 175 - 177°C, yield 76 %

- cont'd -

Table 13 (Cont'd)

	D(-)-  m.p. (decomp.) 177 - 178°C, yield 79 %

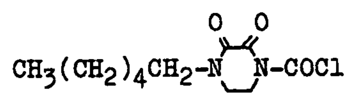
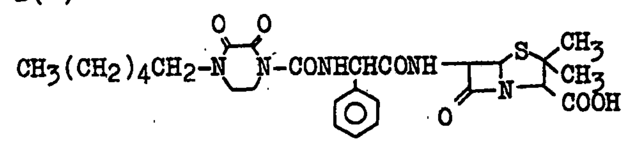
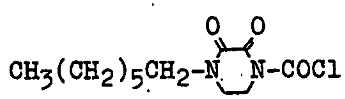
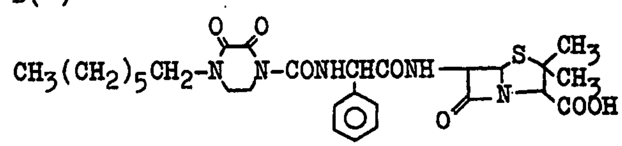
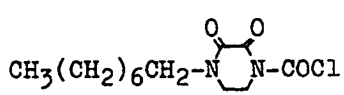
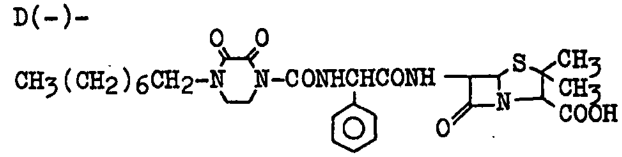
Example 12.

A suspension of 1.4 g of 6-[D(−)-α-aminophenylacetamido]penicillanic acid in 30 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This solution was cooled to 0° to 5°C, and 10 ml of a tetrahydrofuran solution containing 1.2 g of 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride was dropped into said solution. During this period, the pH of the reaction solution was maintained at 7.5 to 8.5 by gradual addition of triethylamine. Subsequently, the resulting mixed solution was reacted at said temperature for 30 minutes and then at 10° to 15°C for 90 minutes, while maintaining the pH thereof at 7.5 to 8.5. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. To the aqueous layer was further added 30 ml of ethyl acetate, and the resulting mixture was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling. Thereafter, the ethyl acetate layer was separated off, sufficiently washed with water, dried over magnesium sulfate, and then freed from the solvent by distillation under reduced pressure. The residue was crystallized by addition of diisopropyl ether to obtain 1.8 g of crystals of 6 - [D(−) - α - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 96°C (decomp.), yield 80.5%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1770 (lactam), 1720—1660 (—CON<, —COOH)
NMR (($(CD_3)_2SO+D_2O$) τ values: 2.62 (5H), 4.31 (1H), 4.51—4.69 (2H), 6.04 (1H), 6.20—6.90 (6H), 8.50 (3H), 8.60 (3H), 8.75 (6H), 8.90 (3H)

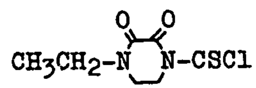
The above-mentioned operation was repeated, except that the 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 14, to obtain respective objective compounds as shown in Table 14. The structure of each objective compound was confirmed by IR and NMR.

Table 14

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 107°C, yield 89 %
	D(-)-  m.p. (decomp.) 92°C, yield 88.5 %
	D(-)-  m.p. (decomp.) 95°C, yield 79.8 %

- cont'd -

Table 14 (Cont'd)

	D(-)-  m.p. (decomp.) 80 - 82°C, yield 95 %

Example 13.

Using 1.7 g of a triethylamine salt of 6-[D(−)-α-amino-p-hydroxyphenylacetamido]penicillanic acid and 0.7 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 11 was repeated to obtain 1.2 g of a sodium salt of 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido]penicillanic acid, m.p. 170—172°C (decomp.), yield 75%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1760 (lactam), 1710—1660 (—CON<), 1600 (—$COO^{\ominus}$)
NMR ($(CD_3)_2SO$) τ values: 2.8—3.3 (4H), 4.45 (1H), 4.65 (2H), 6.05 (1H), 6.2 (4H), 6.97 (3H), 8.48 (3H), 8.60 (3H)

In the same manner as above, a sodium salt of 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-p-hydroxyphenylacetamido]penicillanic acid, m.p. 175°C (decomp.), yield 72%, was obtained from 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride and a triethylamine salt of 6-[D(−)-α-amino-p-hydroxyphenylacetamido]-penicillanic acid.

Example 14.

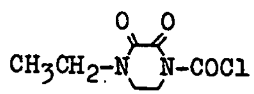
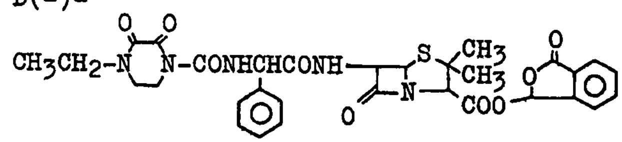
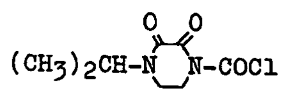
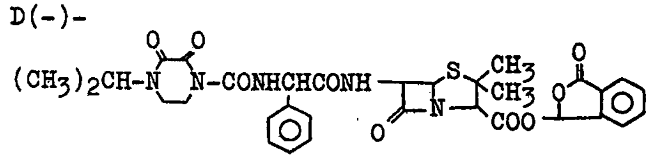
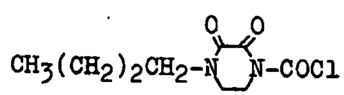
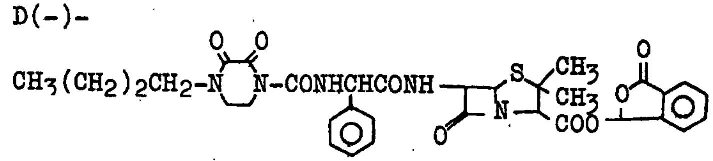
To a solution of 0.8 g of a phthalide ester of 6-[D(−)-α-aminophenylacetamido]-penicillanic acid in 10 ml of tetrahydrofuran was added 0.25 ml of triethylamine. Into the resulting mixture was dropped 0.32 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride with ice-cooling, and the mixture was reacted at room temperature for 2 hours. After the reaction, the solvent was removed by distillation under reduced pressure. The residue was dissolved in a mixed solvent comprising 20 ml of ethyl acetate and 20 ml of water, and the resulting solution was adjusted to a pH of 2 by addition of dilute hydrochloric acid. Subsequently, the organic layer was separated off, washed with water, washed with a 2% aqueous sodium hydrogenocarbonate solution, washed with water,

dried over magnesium sulfate, and then concentrated to a liquid amount of about 2 ml. To the concentrate was added 20 ml of diisopropyl ether to deposit crystals, which were then collected to obtain 0.95 g of crystals of a phthalide ester of 6-[D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 157—160°C (decomp.), yield 90.0%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1715 (ester), 1680 (—CON<)
NMR (($(CD_3)_2CO+D_2O$) τ values: 2.12 (4H), 2.40 (1H), 2.58 (5H), 4.25—4.60 (3H), 5.45 (1H), 5.85—6.42 (4H), 6.90 (3H), 8.50 (6H)

The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 15, to obtain respective objective compounds as shown in Table 15. The structure of each objective compound was confirmed by IR and NMR.

Table 15

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 108 - 110°C, yield 90 %
	D(-)-  m.p. (decomp.) 128 - 130°C, yield 92 %
	D(-)-  m.p. (decomp.) 113 - 115°C, yield 88 %

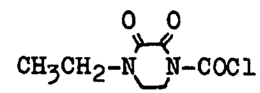
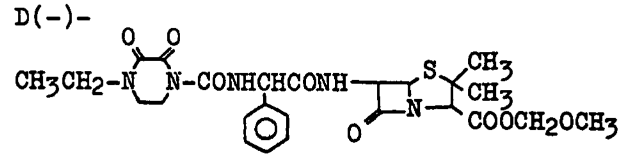
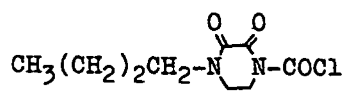
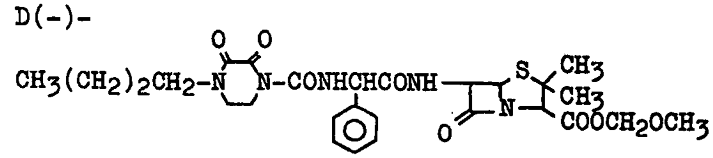
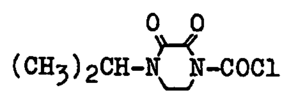
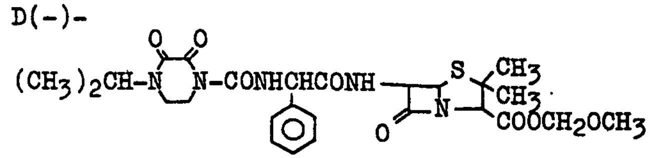
Example 15.

A solution of 0.86 g of a hydrochloride of methoxymethyl ester of 6-[D(−)-α-aminophenylacetamido]penicillanic acid in 15 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine at 0° to 5°C. Into this solution, a solution of 0.38 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride in 10 ml of tetrahydrofuran was dropped over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. The resulting mixed solution was reacted for 30 minutes, while maintaining the pH thereof at 7.5 to 8.0. After completion of the reaction, the tetrahydrofuran was removed by distillation under reduced pressure. The residue was dissolved in a mixed solvent comprising 50 ml of water and 50 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, washed with water, dried over anhydrous magnesium sulfate, and then freed from the solvent by distillation under reduced pressure to form crystals. The thus formed crystals were washed with diethyl ether to obtain 0.9 g of a methoxymethyl ester of 6-[D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 111—115°C (decomp.), yield 82.5%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1740 (ester), 1700—1660 (—CON<)
NMR ($(CD_3)_2CO$) τ values: 0.15 (1H), 2.0 (1H), 2.67 (5H), 4.3—4.5 (3H), 4.75 (2H), 5.7 (1H), 6.55 (4H), 6.97 (3H), 7.25 (3H), 8.84 (3H), 8.60 (3H)

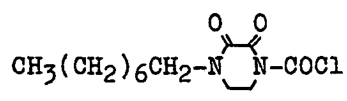
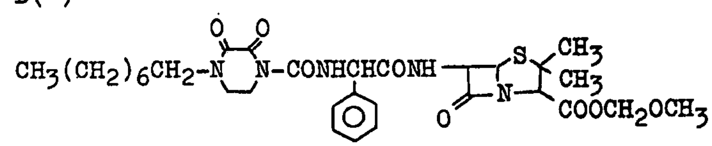
The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 16, to obtain respective objective compounds as shown in Table 16. The structure of each objective compound was confirmed by IR and NMR.

Table 16

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 83 - 85°C, yield 80.2 %
	D(-)-  m.p. (decomp.) 78 - 80°C, yield 80 %
	D(-)-  m.p. (decomp.) 93 - 95°C, yield 82.5 %

- cont'd -

Table 16 (Cont'd)

	D(-)-  m.p. (decomp.) 70 - 74°C, yield 74.4 %

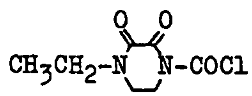
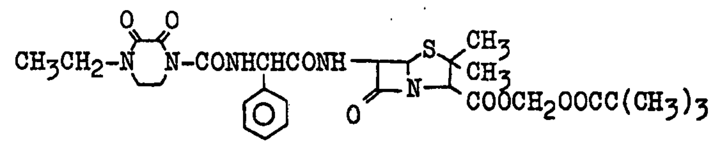
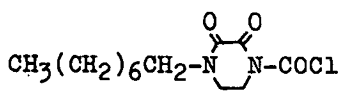
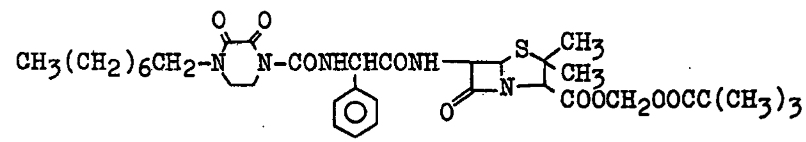
Example 16.

Using 1.5 g of a hydrochloride of pivaloyloxymethyl ester of 6-[D(−)-α-aminophenylacetamido]penicillanic acid and 0.6 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 15 was repeated to obtain a pivaloyloxymethyl ester of 6-[D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetamido]penicillanic acid, m.p. 108—111°C (decomp.), yield 75%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1750 (ester), 1710—1660 (—CON<)

The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 17, to obtain respective objective compounds as shown in Table 17. The structure of each objective compound was confirmed by IR and NMR.

Table 17

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 94 - 98°C, yield 77 %
	D(-)-  m.p. (decomp.) 72 - 75°C, yield 72 %

Example 17.

Using 0.81 g of a hydrochloride of β-piperidinoethyl ester of 6-[D(−)-α-aminophenylacetamido)penicillanic acid and 0.3 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 15 was repeated to obtain 0.75 g of a β-piperidinoethyl ester of 6-[D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetamido]penicillanic acid, m.p. 166—169°C (decomp.), yield 78%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1740 (ester), 1710—1670 (—CON<)
NMR ($CDCl_3$) τ values: 2.7 (5H), 4.3—4.6 (3H), 5.7 (1H), 5.75 (2H), 6.0 (2H), 6.4 (2H), 6.9 (3H), 7.45 (2H), 7.6 (4H), 8.5 (12H)

The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by 4-n-octyl-2,3-dioxo-1-piperazinocarbonyl chloride, to obtain a β-piperidinoethyl ester of 6-[D(−)-α-(4-n-octyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 110—115°C (decomp.), yield 73.58%.

Example 18.

Using 0.93 g of a hydrochloride of β-morpholinoethyl ester of 6-[D(−)-α-aminophenylacetamido]penicillanic acid and 0.39 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 15 was repeated to obtain 0.8 g of a β-morpholinoethyl ester of 6-[D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 150—153°C (decomp.), yield 73%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1740 (ester), 1710—1680 (—CON<)
NMR ($CDCl_3$) τ values: 2.55 (5H), 4.3—4.55 (3H), 5.6 (1H), 5.7 (3H), 6.0 (2H), 6.3 (2H), 7.4 (2H), 7.5 (4H), 8.5 (6H)

The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by 4-n-octyl-2,3-dioxo-1-piperazinocarbonyl chloride, to obtain a β-morpholinoethyl ester of 6-[D(−)-α-(4-n-octyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 103—105°C (decomp.), yield 70%.

Example 19.

(1) To a solution of 8.7 g of a sodium salt of D(−)-α-phenylglycine in 50 ml of water were added 50 ml of ethyl acetate and 5.05 g of triethylamine. To the resulting mixture was gradually added 9.5 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride at 0° to 5°C over a period of 15 minutes, and then the mixture was reacted at 5° to 15°C for 30 minutes. After the reaction, the aqueous layer was separated off, washed with diethyl ether, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit crystals. The deposited crystals were collected by filtration, washed with water and dried to obtain 14.1 g of D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid, m.p. 138—141°C (decomp.), yield 87%. Recrystallization from hydrous butanol gave white crystals, m.p. 140—142°C (decomp.).

Elementary analysis (for $C_{14}H_{15}N_3O_5 . H_2O$):

Calculated (%)	C: 52.01	H: 5.30	N: 13.00
Found (%)	C: 52.24	H: 5.32	N: 12.87

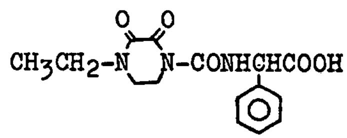
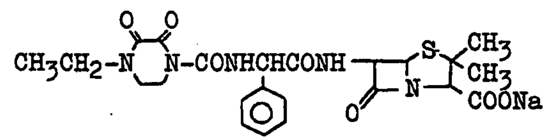
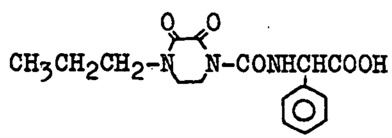
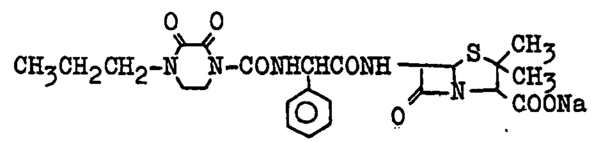
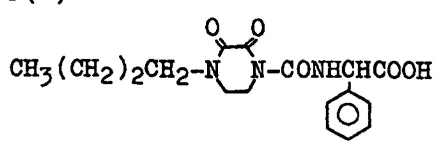
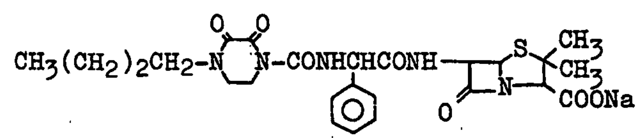
IR (KBr) cm^{-1}: $\nu_{C=O}$ 1710, 1700, 1660

(2) Into a solution of 10 g of the above-mentioned D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid in 200 ml of acetone was dropped a solution of 5.2 g of a sodium salt of 2-ethylhexanoic acid in 50 ml of acetone with stirring to deposit crystals. The deposited crystals were collected by filtration and then washed with acetone to obtain 9.6 g of a sodium salt of D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid, m.p. 165°C (decomp.), yield 95%.

(3) To a suspension of 8.8 g of the above-mentioned sodium salt of D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid in 80 ml of methylene chloride was added 20 mg of N-methylmorpholine. Into the resulting mixture was dropped a solution of 3.1 g of ethyl chlorocarbonate in 20 ml of methylene chloride at −20° to −15°C over a period of 5 minutes, and the mixture was reacted at said temperature for 1 hour. Into this reaction liquid was dropped a solution of 9.4 g of a triethylamine salt of 6-aminopenicillanic acid in 40 ml of methylene chloride at −40° to −30°C over a period of 10 minutes, and the resulting mixture was reacted at −40° to −20°C over a period of 1 hour. After the reaction, the temperature of the reaction liquid was gradually elevated to 0°C over a period of 1 hour, and the mixture was then subjected to extraction with 100 ml of water. Subsequently, the aqueous layer was separated off, and the methylene chloride layer was further subjected to extraction with 50 ml of water, and the resulting aqueous layer was combined with the aforesaid aqueous layer. The combined aqueous layer was adjusted to a pH of 2 by addition of dilute hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration, sufficiently washed with water, dried and then dissolved in 200 ml of acetone. Into the resulting solution was dropped a solution of 4 g of a sodium salt of 2-ethylhexanoic acid in 40 ml of acetone over a period of 10 minutes to deposit crystals. The deposited crystals were collected by filtration, washed with acetone and then dried to obtain 11.4 g of a sodium salt of 6-[D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 170°C (decomp.), yield 80.8%.

The above-mentioned operation was repeated, except that the D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 18, to obtain respective objective compounds as shown in Table 18. The structure of each objective compound was confirmed by IR and NMR.

Table 18

Compound of formula (V)	Objective compound
D(-)- 	D(-)- 
D(-)- 	D(-)- 
D(-)- 	D(-)- 

Example 20.

(1) To a solution of 2.28 g of D(−)-α-amino-1,4-cyclohexadienylacetic acid in 15 ml of N NaOH were added 20 ml of ethyl acetate and 2.1 ml of triethylamine, and the resulting mixture was cooled to 0°C. To this mixture was gradually added 1.69 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. Subsequently, the mixture was reacted for 30 minutes with ice-cooling, and then the aqueous layer was separated off. To the aqueous layer was further added 20 ml of ethyl acetate. The resulting mixture was adjusted to a pH of 2 by addition of 2N hydrochloric acid with ice-cooling, and the ethyl acetate layer was separated off. The organic layer was sufficiently washed with water, dried over anhydrous magnesium sulfate, freed from the solvent by distillation under reduced pressure and then incorporated with isopropyl alcohol to deposit crystals. The deposited crystals were collected by filtration to obtain 2.5 g of white crystals of D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid, m.p. 140—145°C (decomp.), yield 74%.

IR (KBr) cm^{-1}: ν_{NH} 3300, $\nu_{C=O}$ 1715, 1660
NMR (d_6-DMSO) τ values: 0.57 (1H, d), 4.26 (1H, s), 4.36 (2H, s), 5.29 (1H, d), 6.07—6.18 (2H, m), 6.38—6.49 (2H, m), 7.05 (3H, s), 7.35 (4H, s)

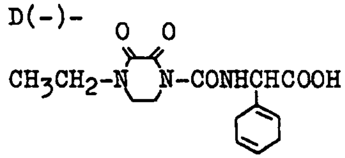
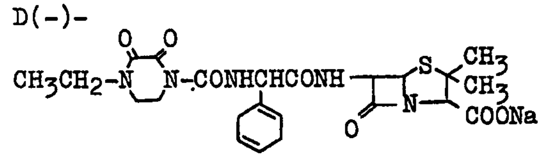
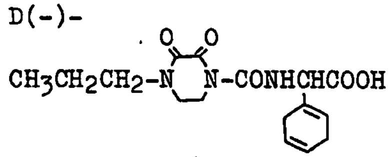
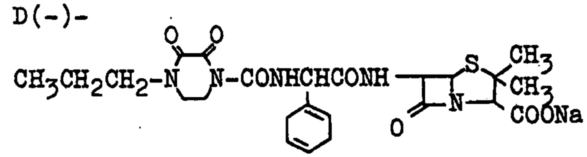
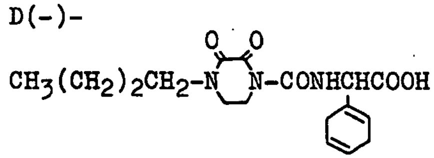
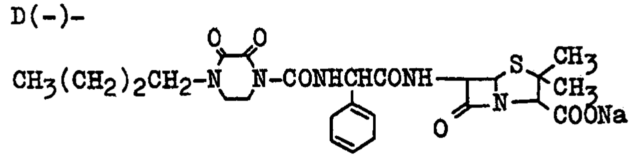
(2) To a suspension of 0.45 g of the above-mentioned D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid in 15 ml of anhydrous methylene chloride was added 0.24 ml of N-methylmorpholine with stirring to form a solution. After cooling the solution of −10°C, 3 ml of an anhydrous methylene chloride solution containing 0.24 g of ethyl chlorocarbonate was dropped into the solution, and the resulting mixture was reacted at said temperature for 90 minutes. Subsequently, the reaction liquid was cooled to −20°C, and 5 ml of a methylene chloride solution containing 0.70 g of a triethylamine salt of 6-aminopenicillanic acid and 0.31 ml of triethylamine was gradually dropped into the reaction liquid. The resulting mixture was reacted at −20°C for 1 hour, at −20° to 0°C for 1 hour, and at 0° to 5°C for 1 hour. Thereafter, the reaction liquid was freed from the solvent by distillation under reduced pressure. The residue was dissolved in 10 ml of water and then washed with 10 ml of ethyl acetate. The aqueous layer was again incorporated with 15 ml of ethyl acetate, and then adjusted to a pH of 2.0 by addition of 2N HCl with ice-cooling. Subsequently, the ethyl acetate layer was separated off, washed with water, dried over anhydrous magnesium sulfate, and freed from the solvent by distillation under reduced pressure to obtain 0.74 g of white crystals of 6-[D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetamido]penicillanic acid, m.p. 84—87°C (decomp.), yield 87%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1730—1660 (—COOH, —CON<)
NMR (d_6-DMSO) τ values: 0.55 (1H, d), 0.95 (1H, d), 4.22 (1H, s), 4.35 (2H, s), 4.41—4.61 (2H, s), 4.92 (1H, d), 5.75 (1H, s), 6.05 (2H, bs), 6.40 (2H, bs), 7.03 (3H, s), 7.35 (4H, s), 8.40 (3H, s), 8.52 (3H, s)

The thus obtained product was adjusted to a pH of 7.0 by neutralization with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt thereof.

The above-mentioned operation was repeated, except that the D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid was replaced by each of the compounds of formula (V) shown in Table 19, to obtain respective objective compounds as shown in Table 19. The structure of each objective compound was confirmed by IR and NMR.

Table 19

Compound of formula (V)	Objective compound
D(-)- 	D(-)- 
D(-)- 	D(-)- 
D(-)- 	D(-)- 

Example 21.

(1) To a solution of 2.2 g of DL-α-amino-2-thienylacetic acid in 14 ml of a N sodium hydroxide solution was added at 0°C 2.2 g of triethylamine. To the resulting mixture was further added 3.6 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride little by little at said temperature. Subsequently, the mixture was reacted at 0°C for 30 minutes, and then at room temperature for 30 minutes. After the reaction, the reacion liquid was adjusted to a pH of 1.0 by addition of dilute hydrochloric acid to deposit crystals. The deposited crystals were collected by filtration, washed with water and then dried to obtain 3.5 g of DL-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid, m.p. 214—215°C (decomp.), yield 80.5%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1710, 1680—1660

(2) Into a solution of 3.5 g of the above-mentioned DL-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid in 100 ml of acetone was dropped a solution of 1.86 g of a sodium salt of 2-ethylhexanoic acid in 50 ml of acetone, upon which crystals were deposited. The deposited crystals were collected by filtration and then washed with acetone to obtain 3.5 g of a sodium salt of DL-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid, m.p. 175—176°C (decomp.).

(3) To a suspension of 3.3 g of the above-mentioned sodium salt of DL-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid in 50 ml of methylene chloride was added 30 mg of N-methylmorpholine, and the resulting mixture was then cooled to −20° to −15°C. Into the resulting mixture was dropped a solution of 1.3 g of ethyl chlorocarbonate in 20 ml of methylene chloride over a period of 5 minutes, and the mixture was stirred at said temperature for 90 minutes. Subsequently, a solution of 3.3 g of a triethylamine salt of 6-aminopenicillanic acid in 50 ml of methylene chloride was dropped into the mixture at −50° to −40°C over a period of 20 minutes, and the resulting mixture was reacted with stirring at −40° to −30°C for 30 minutes, at −30° to −20°C for 30 minutes, and then at −20° to 0°C for 30 minutes. After the reaction, the solvent was removed by distillation under reduced pressure, and the residue was dissolved in water. The resulting aqueous solution was adjusted to a pH of 2.0 by addition of dilute hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.1 g of 6-[DL-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetamido]penicillanic acid, m.p. 185°C (decomp.), yield 80.5%.

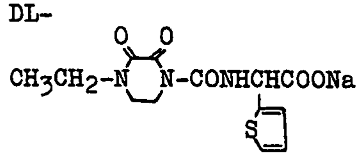
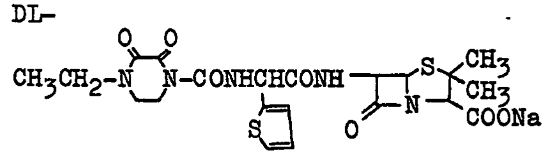
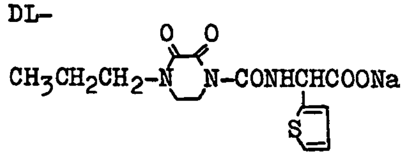
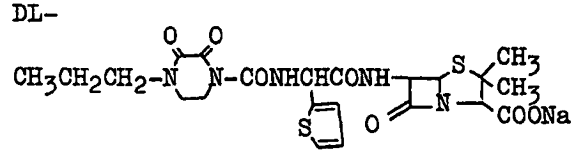
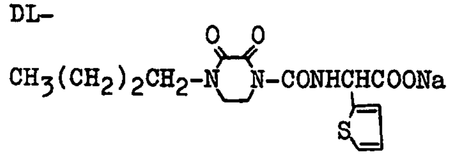
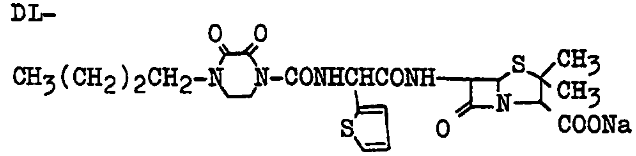
IR (Nujol Registered Trade Mark) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1715 (—COOH), 1685—1675 (—CON<)

NMR ($(CD_3)_2CO$) τ values: 0.5 (1H), 1.8 (1H), 2.6 (1H), 2.85—3.05 (2H), 4.0 (1H), 4.2—4.5 (2H), 5.7 (1H), 5.8—6.0 (2H), 6.2—6.4 (2H), 6.95 (3H), 8.4 (3H), 8.45 (3H)

The thus obtained product was adjusted to a pH of 7.0 by neutralization with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt thereof.

The above-mentioned operation was repeated, except that the sodium salt of DL-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid was replaced by each of the compounds of formula (V) shown in Table 20, to obtain respective objective compounds as shown in Table 20. The structure of each objective compound was confirmed by IR and NMR.

Table 20

Compound of formula (V)	Objective compound
DL- 	DL- 
DL- 	DL- 
DL- 	DL- 

Example 22.

To a suspension of 0.9 g of 6-[D(−)-α-aminophenylacetamido]penicillanic acid in 30 ml of anhydrous ethyl acetate were added at 5° to 10°C 0.55 g of triethylamine and 0.6 g of trimethylsilyl chloride. The resulting mixture was reacted at 15° to 20°C for 3 hours to form trimethylsilylated 6-[D(−)-α-aminophenylacetamido]penicillanic acid. To this acid was then added 1 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride, and the resulting mixture was reacted at 15° to 20°C for 2 hours. After the reaction, a deposited triethylamine hydrochloride was separated by filtration, and the filtrate was incorporated with 0.4 g of n-butanol to deposit crystals. The deposited crystals were collected by filtration to obtain 1.25 g of white crystals of 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid. Into a solution of said crystals in 30 ml of tetrahydrofuran was dropped a solution of 0.38 g of a sodium salt of 2-ethylhexanoic acid in 10 ml of tetrahydrofuran, upon which white crystals were deposited. The deposited crystals were collected by filtration, sufficiently washed with tetrahydrofuran and then dried to obtain 1.25 g of a sodium salt of 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 183—185°C (decomp.), yield 90%.

Example 23.

To a suspension of 4 g of a trihydrate of 6-[D(−)-α-aminophenylacetamido]-penicillanic acid in 40 ml of water was added 20 ml of ethyl acetate, and the resulting mixture was cooled to 2°C. Subsequently, the mixture was incorporated with 1.37 g of potassium carbonate, and then stirred at 2° to 3°C for 2 minutes. Thereafter, 1.89 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was added to the mixture at said temperature over a period of 10 minutes, and the resulting mixture was reacted at said temperature for 15 minutes. After the reaction, slight amounts of insolubles were separated by filtration, and the filtrate was charged into 80 ml of ethyl acetate. Into the resulting mixture was dropped 5 ml of 2N HCl at 20° to 22°C over a period of 5 minutes, and the mixture was stirred at said temperature for 5 hours to deposit crystals. The deposited crystals were collected by filtration, washed two times with 4 ml of water, further washed two times with 4 ml of isopropanol, and then dried to obtain 4.0 g of a dihydrate of 6-[D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 156—157°C (decomp.), yield 75.4%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1775, 1740, 1695, 1670
NMR (d_6-DMSO) τ values: 0.18 (1H, d), 0.77 (1H, d), 2.66 (5H, s), 4.30 (1H, d), 4.40 (3H, br), 4.48 (1H, g), 4.65 (1H, d), 5.80 (1H, s), 6.12 (2H, bs), 6.45 (2H, bs), 7.06 (3H, s), 8.48 (3H, s), 8.60 (3H, s)

The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride, to obtain a monohydrate of 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 154—156°C (decomp.), yield 84.8%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1775, 1735, 1705, 1680, 1665
NMR (d_6-DMSO) τ values: 0.20 (1H, d), 0.76 (1H, d), 2.69 (5H, s), 4.32 (1H, d), 4.53 (1H, q), 4.64 (1H, d), 5.00 (3H, br), 5.83 (1H, s), 6.13 (2H, bs), 6.49 (2H, bs), 6.62 (2H, q), 8.44 (3H, s), 8.58 (3H, s), 8.91 (3H, t)

The thus obtained monohydrate was neutralized with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt of 6-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]-penicillanic acid.

Further, a solution in 10 ml of nitromethane of 2 g of the aforesaid dihydrate of 6-[D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid was allowed to stand overnight to deposit crystals, which were then collected by filtration to obtain 2 g of a monohydrate of a nitromethane addition product of 6-[D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 128—130°C (decomp.), yield 92.2%.

Elementary analysis (for $C_{22}H_{25}N_5O_7S \cdot CH_3NO_2 \cdot H_2O$):

Calculated (%)	C: 47.42	H: 5.19	N: 14.43
Found (%)	C: 47.94	H: 5.13	N: 14.53

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1770, 1735, 1700, 1680
NMR (d_6-DMSO) τ values: 0.22 (1H, d), 0.80 (1H, d), 2.69 (5H, s), 3.30 (3H, br), 4.30 (1H, d), 4.46—4.70 (2H), 5.67 (3H, s), 5.81 (1H, s), 6.13 (2H, bs), 6.46 (2H, bs), 7.07 (3H, s), 8.45 (3H, s), 8.58 (3H, s)

Example 24.

To a suspension of 1.6 g of a trihydrate of D(−)-α-aminobenzyl penicillin in 20 ml of water was added at 2° to 3°C 0.54 g of potassium carbonate, and the resulting mixture was stirred for 3 minutes. To the mixture was gradually added 0.81 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride at said temperature over a period of 10 minutes, and the mixture was reacted for 15 minutes. After the reaction, slight amounts of insolubles formed were separated by filtration, and the filtrate was charged into 10 ml of methyl n-propyl ketone. Into the resulting mixture was dropped 1.98 ml of 2N HCl at 15° to 20°C over a period of 2 minutes, and the mixture was stirred at said temperature for 1 hour to deposit crystals. The deposited crystals were collected by filtration, washed two times with 2 ml of water, further washed two times with 2 ml of methyl n-propyl ketone, and then dried to obtain 1.7 g of a monohydrate of D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)benzylpenicillin, m.p. 152—154°C (decomp.), yield 80.2%.

The thus obtained product was neutralized with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt of the said product.

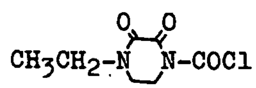
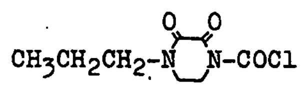
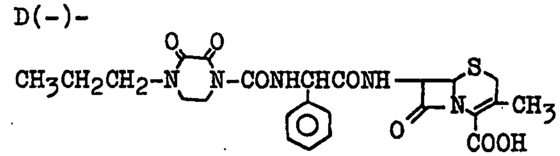
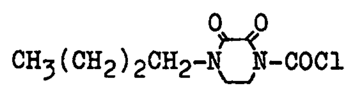
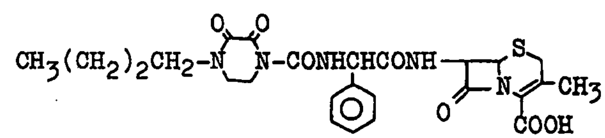
Example 25.

A suspension of 4.0 g of a monohydrate of 7-[D(−)-α-aminophenylacetamido]-3-methyl-Δ^3-cephem-4-carboxylic acid in 60 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the reaction liquid was stirred together with 60 ml of diethyl ether and 70 ml of water, and then the aqueous layer was separated off. The thus obtained aqueous layer was washed with 30 ml of ethyl acetate, cooled to 0° to 5°C, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.7 g of white crystals of 7 - [D(−) - α-(4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl-Δ^3 - cephem - 4 - carboxylic acid, m.p. 185—186°C (decomp.), yield 86%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1770—1760 (lactam), 1720—1660 (—CON<, —COOH)
NMR (d_6-DMSO) τ-values: 0.1 (1H, d), 0.56 (1H, d), 2.62 (5H, s), 4.26—4.37 (2H, dd), 5.05 (1H, d), 6.1 (2H, bs), 6.47 (2H, bs), 6.63 (2H, s), 7.05 (3H, s), 8.02 (3H, s)

The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 21, to obtain respective objective compounds as shown in Table 21. The structure of each objective compound was confirmed by IR and NMR.

Table 21

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 168°C, yield 80 %
	D(-)-  m.p. (decomp.) 160°C, yield 80.5 %
	 m.p. (decomp.) 150°C, yield 76 %

Example 26.

(1) To a solution of 0.92 g of 1-n-pentyl-2,3-dioxo-piperazine in 15 ml of anhydrous dioxane were added 1.1 ml of triethylamine and 1.08 g of trimethylsilyl chloride. The resulting mixture was stirred at room temperature for 20 hours to form triethylamine hydrochloride. This hydrochloride was separated by filtration, and the filtrate was dropped at 0° to 5°C into a solution of 0.6 g of phosgene in 10 ml of anhydrous tetrahydrofuran. Subsequently, the resulting mixture was reacted at 5° to 10°C for 30 minutes and then at room temperature for 2 hours. Thereafter, the solvent was removed by distillation under reduced pressure to obtain 1.21 g of pale yellow, oily 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride.

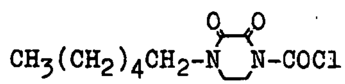
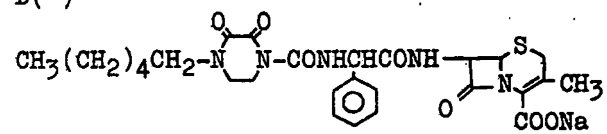
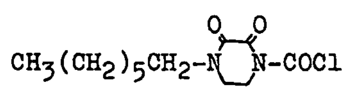
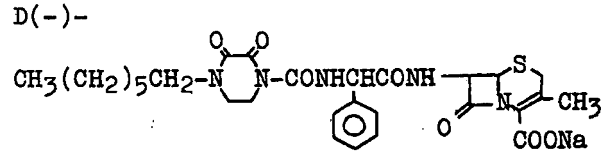
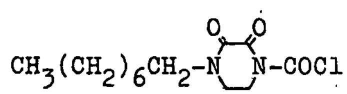
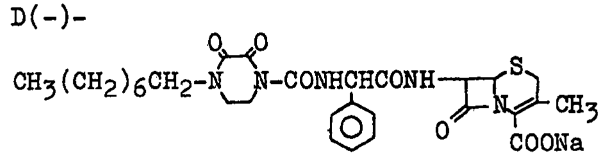
IR (film) cm^{-1}: $\nu_{C=O}$ 1790, 1720—1665

(2) A suspension of 1.70 g of a monohydrate of 7-[D(−)-α-aminophenylacetamido]-3-methyl-Δ^3-cephem-4-carboxylic acid in 50 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This solution was cooled to 0° to 5°C, and 7 ml of an anhydrous tetrahydrofuran solution containing 1.21 g of the 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride obtained in (1) was dropped into the solution. During this period, the pH of the solution was maintained at a pH of 7.5 to 8.0 by addition of triethylamine. Subsequently, the resulting mixed solution was reacted at 0° to 5°C for 1 hour and then at 5° to 10°C for 2 hours while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. The aqueous layer was again charged with 40 ml of ethyl acetate, and then adjusted to a pH of 1.5 by gradual addition of dilute hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, washed with water, and then dried over anhydrous magnesium sulfate. Thereafter, 10 ml of an ethyl acetate solution containing 0.75 g of sodium 2-ethylhexanoate was dropped into the layer at 0° to 5°C to deposit white crystals. The deposited crystals were collected by filtration, and washed with ethyl acetate and then with diethyl ether to obtain 1.95 g of a sodium salt of 7 - [D(−) - α - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, m.p. 164—166°C (decomp.), yield 75%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1750 (lactam), 1720—1660 (—CON<), 1590 (—$COO^{\ominus}$)
NMR (d_6-DMSO+D_2O) τ values: 2.58 (5H, s), 4.33 (1H, s), 4.49 (1H, d), 5.17 (1H, d), 6.10 (2H, bs), 6.42—6.87 (6H, m), 8.09 (3H, s), 8.60—8.90 (6H, bs), 9.12 (3H, t)

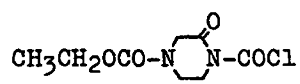
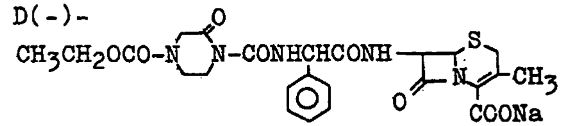
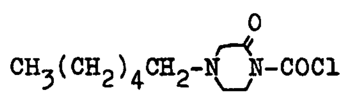
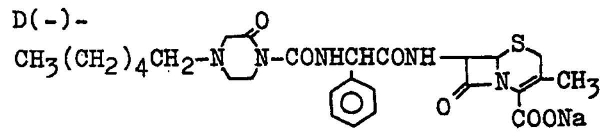
The above-mentioned operation was repeated, except that the 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 22, to obtain respective objective compounds as shown in Table 22. The structure of each objective compound was confirmed by IR and NMR.

Table 22

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 160°C, yield 77.7 %
	D(-)-  m.p. (decomp.) 158°C, yield 78 %
	D(-)-  m.p. (decomp.) 154°C, yield 78 %

- cont'd -

Table 22 (Cont'd)

	D(-)-  m.p. (decomp.) 185 - 188°C, yield 77 %
	D(-)-  m.p. (decomp.) 135 - 137°C, yield 79.2 %

Example 27.

Using 1.5 g of a hydrochloride of methoxymethyl ester of 7-[D(−)-α-aminophenylacetamido]-3-methyl-Δ^3-cephem-4-carboxylic acid and 0.65 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 25 was repeated to obtain 1.6 g of a methoxymethyl ester of 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4-carboxylic acid, m.p. 146—148°C (decomp.), yield 86%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1770 (lactam), 1710 (ester), 1680—1600 (—CON<)

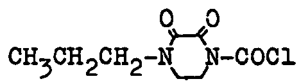
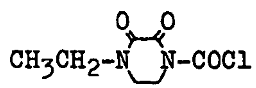
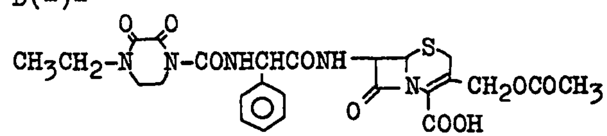
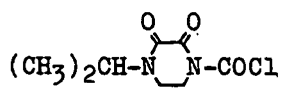
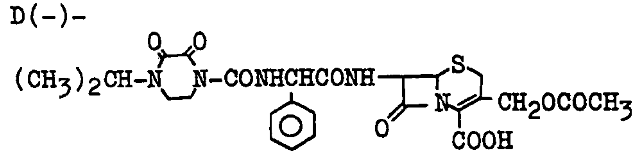
Example 28.

To a suspension of 0.20 g of 7-[D(−)-α-aminophenylacetamido]-3-acetoxymethyl-Δ^3-cephem-4-carboxylic acid in 15 ml of anhydrous chloroform was added 0.17 ml of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution was added 0.11 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, and the resulting mixture was reacted at room temperature for 2 hours. After the reaction, the reaction liquid was evaporated under reduced pressure, and the residue was dissolved in 15 ml of water. The resulting solution was washed with 10 ml of ethyl acetate. The aqueous layer was again charged with 20 ml of ethyl acetate, and then adjusted to a pH of 1.5 by addition of 2N hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, successively washed with water and a saturated aqueous sodium chloride solution, and then dried over magnesium sulfate. Thereafter, the solvent was removed by distillation under reduced pressure to obtain 0.22 g of white crystals of 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, m.p. 175°C (decomp.), yield 76%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1770 (lactam), 1720—1650 (—CON<, —COOH)
NMR (d_6-DMSO) τ values: 0.23 (1H, d), 0.63 (1H, d), 2.66 (5H, s), 4.32 (1H, q), 4.43 (1H, d), 5.05 (1H, d), 5.21 (2H, q), 6.15 (2H, bs), 6.40 (2H, bs), 6.57 (2H, bs), 7.0 (3H, s), 8.0 (3H, s)

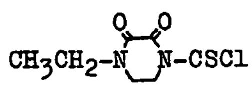
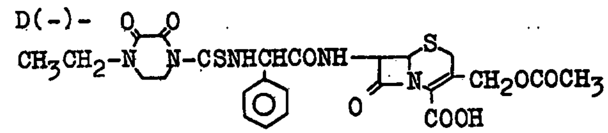
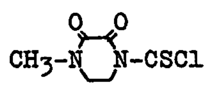
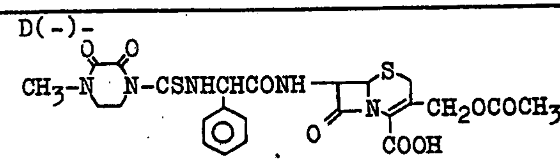
The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 23, to obtain respective objective compounds as shown in Table 23. The structure of each objective compound was confirmed by IR and NMR.

Table 23

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-  m.p. (decomp.) 150°C, yield 83.4 %
	D(-)-  m.p. (decomp.) 165°C, yield 83 %
	D(-)-  m.p. (decomp.) 146°C, yield 82 %

- cont'd -

Table 23 (Cont'd)

	 m.p. (decomp.) 112°C, yield 95 %
	 m.p. (decomp.) 134°C, yield 90.2 %

The aforesaid 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, m.p. 175°C (decomp.), was recrystallized from hydrous acetone to obtain white crystals showing a melting point of 198° to 200°C (decomp.).

Example 29.

(1) To a solution of 28.2 g of a sodium salt of D(−)-phenylglycine in 150 ml of water were added 200 ml of ethyl acetate and 18.2 g of triethylamine, and the resulting mixture was cooled to 0°C. To this mixture was added 34.3 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 15 minutes, and the mixture was reacted at 5° to 10°C for 15 minutes. Thereafter, the aqueous layer was separated off and adjusted to a pH of 0.5 by addition of 2N hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration and then dried to obtain 42 g of white crystals of D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid.

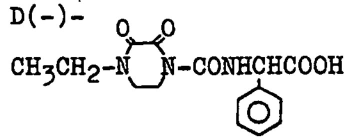
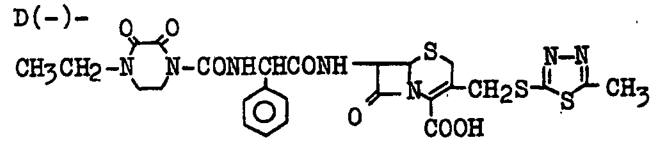
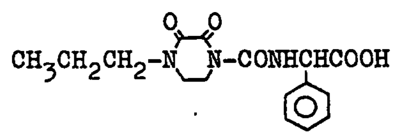
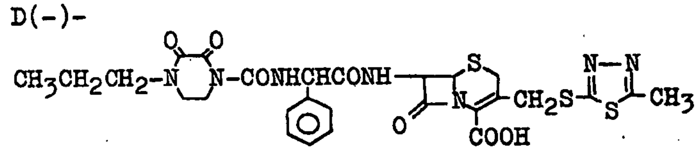
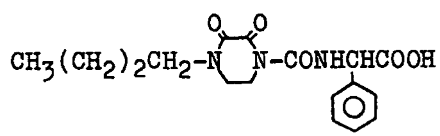
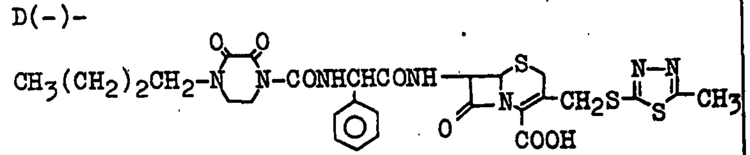
(2) To a suspension in 15 ml of anhydrous methylene chloride of 0.31 g of the D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid obtained in the above-mentioned item (1) was added 0.11 g of N-methylmorpholine with stirring to form a solution, which was then cooled to −20°C. To this solution was added 3 ml of an anhydrous methylene chloride solution containing 0.13 g of ethyl chlorocarbonate, and the resulting mixture was reacted at −10°C to −20°C for 60 minutes

to form a mixed acid anhydride. Into the thus formed acid anhydride was dropped a solution formed by adding 0.50 ml of triethylamine to a suspension in 5 ml of methanol of 0.41 g of 7 - amino - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl]- Δ^3 - cephem - 4 - carboxylic acid. After the dropping, the resulting mixture was reacted at −50° to −30°C for 30 minutes, at −30° to −20°C for 30 minutes, at −20° to 0°C for 60 minutes, and then at room temperature for 30 minutes. Thereafter, the reaction liquid was concentrated under reduced pressure, and the concentrate was dissolved in 10 ml of water, washed with 5 ml of ethyl acetate, again charged with 15 ml of ethyl acetate, and then adjusted to a pH of 1.5 by addition of 2N hydrochloric acid with ice-cooling. Subsequently, insolubles were separated by filtration, and the ethyl acetate layer was separated off, successively washed with water and a saturated sodium chloride solution, dried over magnesium sulfate, and then freed from the solvent by distillation under reduced pressure to obtain 0.58 g of pale yellow crystals of 7 - [D(−)- α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2-(5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, m.p. 160°C (decomp.), yield 91%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1650—1720 (—CON<, —COOH)
NMR (d_6-DMSO) τ values: 0.2 (1H, d), 0.6 (1H, d), 2.60 (5H, s), 4.35 (1H, q), 4.40 (1H, d), 5.0 (1H, d), 5.70 (2H, q), 6.10 (2H, bs), 6.25—6.55 (2H, 2H, bs), 7.0 (3H, s), 7.30 (3H, s)

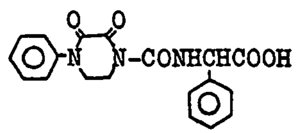
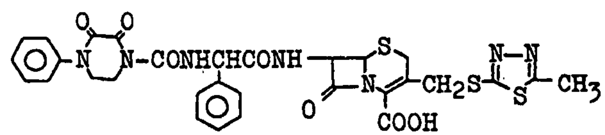
The above-mentioned operation was repeated, except that the D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 24, to obtain respective objective compounds as shown in Table 24. The structure of each objective compound was confirmed by IR and NMR.

Table 24

Compound of formula (V)	Objective compound
D(-)- 	D(-)-  m.p. (decomp.) 150°C, yield 91 %
D(-)- 	D(-)-  m.p. (decomp.) 147°C, yield 85.4 %
D(-)- 	D(-)-  m.p. (decomp.) 144°C, yield 84.3 %

- cont'd -

Table 24 (Cont'd)

D(-)- 	D(-)-  m.p. (decomp.) 167°C, yield 93 %

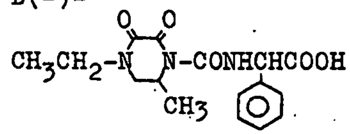
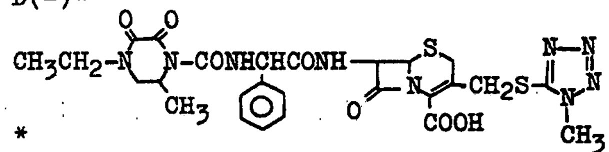
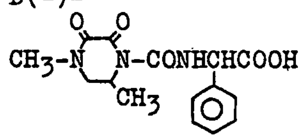
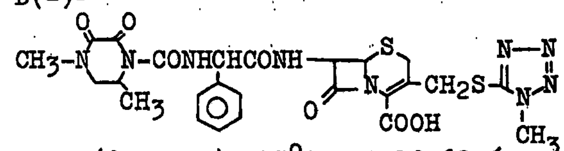
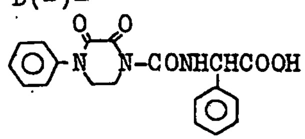
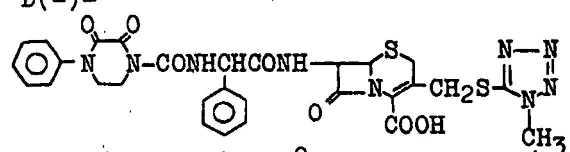
Example 30.

Using 0.3 g of D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid and 0.33 g of 7 - amino - 3 - [5 - (1 - methyl - 1,2,3,4-tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, the same operation as in Example 29 was repeated, to obtain 0.5 g of 7 - [D(−) - α - (4 - methyl-2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl-1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, m.p. 161—163°C (decomp.), yield 76%.

IR (nujol) cm^{-1}: $\nu_{C=O}$ 1775 (lactam), 1720—1660 (—CON<, —COOH)
NMR (d_6-DMSO) τ values: 0.02 (1H, d), 0.34 (1H, d), 2.48 (5H, s), 4.17 (1H, q), 4.26 (1H, d), 4.92 (1H, d), 5.66 (2H, s), 6.01 (5H, s), 6.35 (4H, s), 7.0 (3H, s)

The above-mentioned operation was repeated, except that the D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 25, to obtain respective objective compounds as shown in Table 25. The structure of each objective compound was confirmed by IR and NMR.

Table 25

Compound of formula (V)	Objective compound
D(-)- 	D(-)-  * m.p. (decomp.) 170°C, yield 63.6 %
D(-)- 	D(-)-  m.p. (decomp.) 173°C, yield 68 %
D(-)- 	D(-)-  m.p. (decomp.) 163°C, yield 74.8 %

* Anhydrous methylene chloride was substituted for the methanol used in Example 29.

Example 31.

Using 0.30 g of D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid and 0.34 g of 7 - amino - 3 - [5 - (1,3,4 - thiadiazolyl)-thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, the same operation as in Example 29 was repeated, to obtain 0.47 g of 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1-piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, m.p. 158—159°C (decomp.), yield 71.5%.

IR (nujol) cm^{-1}: $\nu_{C=O}$ 1775 (lactam), 1720—1660 (—CON<, —COOH)

The above-mentioned operation was repeated, except that the D(−) - α-(4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid was replaced by D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetic acid, to obtain 7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl]-Δ^3 - cephem - 4 - carboxylic acid, m.p. 123°C (decomp.), yield 64.5%.

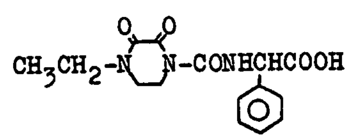
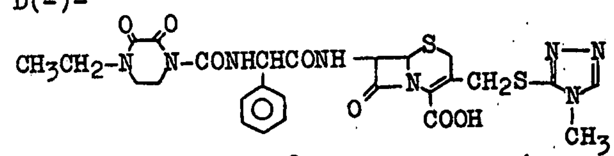
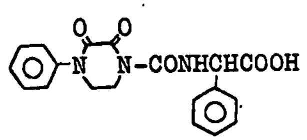
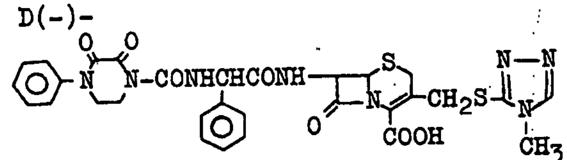
Example 32.

Using 0.31 g of D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid and 0.39 g of 7 - amino - 3 - [2 - (1 - methyl - 1,3,4-triazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, the same operation as in Example 29 was repeated, except that the methanol was replaced by anhydrous methylene chloride, to obtain 0.43 g of 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1-piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl)-thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, yield 70%.

IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1720—1650 (—CON<, —COOH)

The above-mentioned operation was repeated, except that the D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 26, to obtain respective objective compounds as shown in Table 26. The structure of each objective compound was confirmed by IR and NMR.

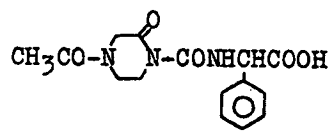
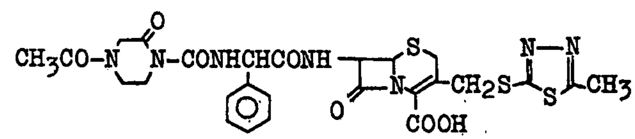
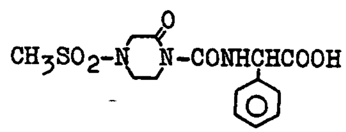
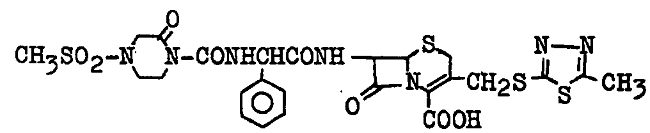
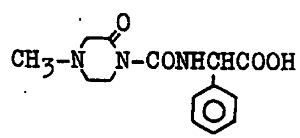
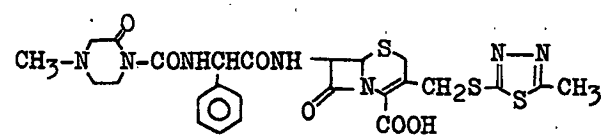
Table 26

Compound of formula (V)	Objective compound
D(-)- 	D(-)-  m.p. (decomp.) 147°C, yield 68.5 %
D(-)- 	D(-)-  m.p. (decomp.) 158°C, yield 74.5 %

Example 33.

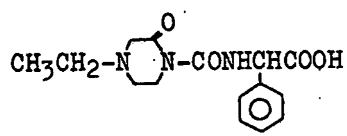
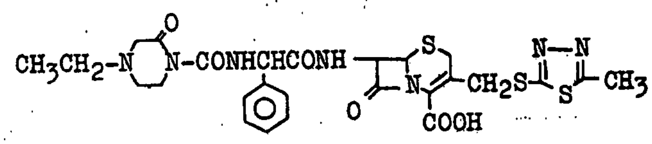
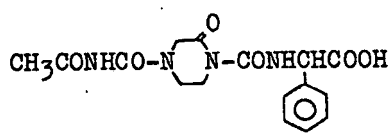
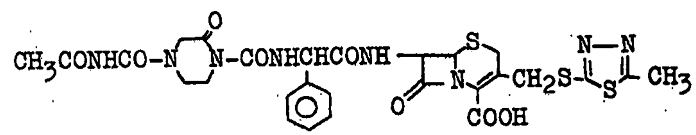
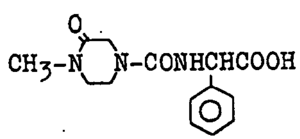
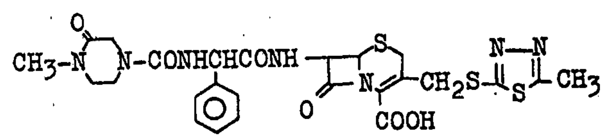
The procedure of Example 29 was repeated, except that the D(—)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 27, to obtain respective objective compounds shown in Table 27. The structure of each objective compound was confirmed by IR and NMR.

Table 27

Compound of formula (V)	Objective compound
D(-)- 	D(-)- 
D(-)- 	D(-)- 
D(-)- 	D(-)- 

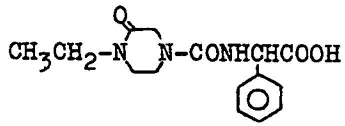
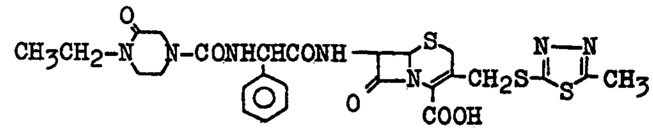
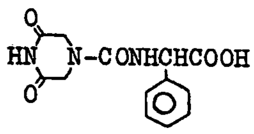
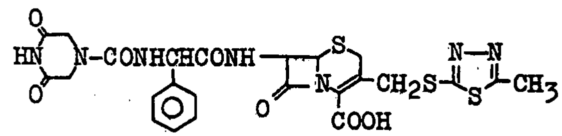
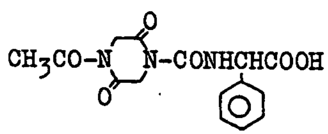
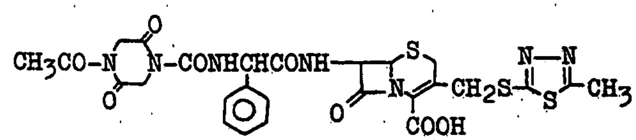
- cont'd -

Table 27 (Cont'd)

D(-)- 	D(-)- 
D(-)- 	D(-)- 
D(-)- 	D(-)- 

- cont'd -

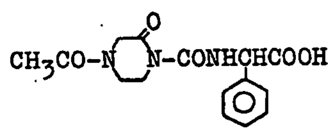
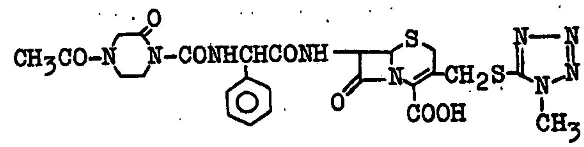
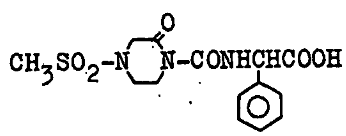
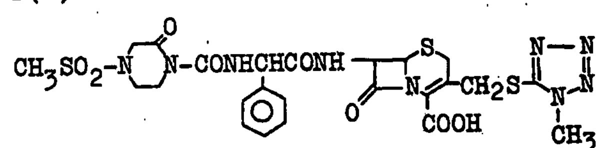
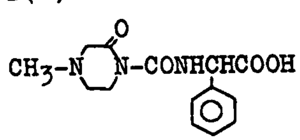
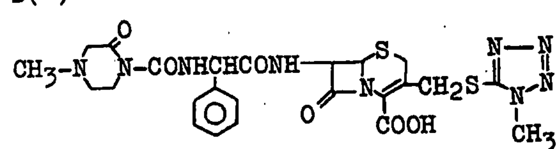
Table 27 (Cont'd)

D(-)- 	D(-)- 
D(-)- 	D(-)- 
D(-)- 	D(-)- 

Example 34.

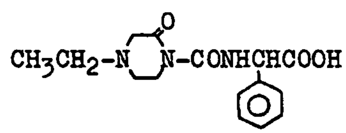
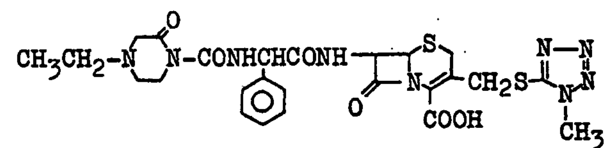
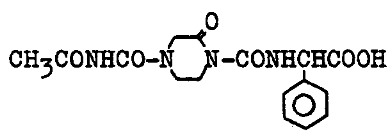
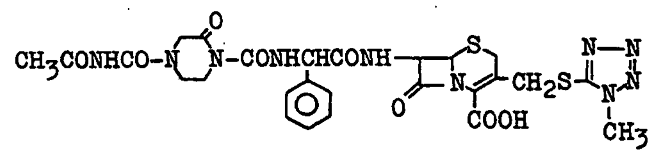
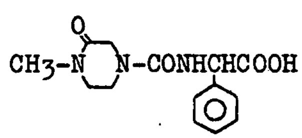
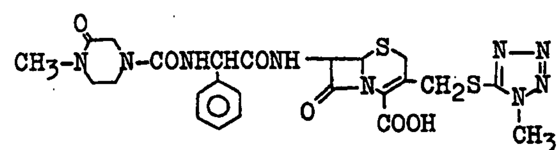
The procedure of Example 30 was repeated, except that the D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 28, to obtain respective objective compounds shown in Table 28. The structure of each objective compound was confirmed by IR and NMR.

Table 28

Compound of formula (V)	Objective compound
D(-)- 	D(-)- 
D(-)- 	D(-)- 
D(-)- 	D(-)- 

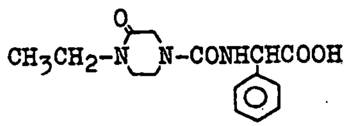
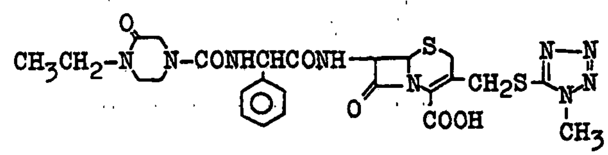
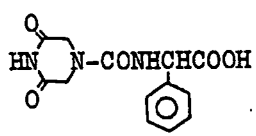
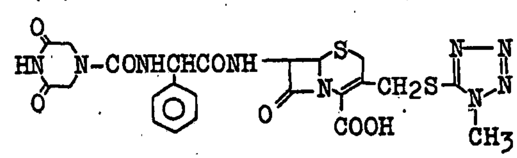
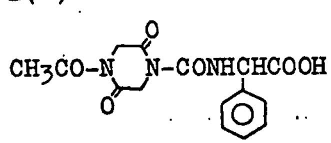
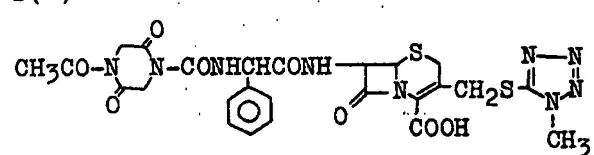
- cont'd -

Table 28 (Cont'd)

D(-)- 	D(-)- 
D(-)- 	D(-)- 
D(-)- 	D(-)- 

- cont'd -

Table 28 (Cont'd)

D(-)- 	D(-)- 
D(-)- 	D(-)- 
D(-)- 	D(-)- 

Example 35.

(1) To a suspension of 0.9 g of D(−)-α-alanine in 15 ml of water was added 2.05 g of triethylamine to dissolve D(−)-α-alanine in water, and the resulting solution was cooled to 0°C. To the solution was added 2.3 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over 15 minutes, after which reaction was effected for 30 minutes with ice-cooling. Dilute hydrochloric acid was then added to the reaction product to adjust the pH thereof to 2.0. The water was removed by distillation under reduced pressure. and 30 ml of acetone was added to the residue, after which insolubles were filtered off. To the resulting acetone solution was added 10 ml of an acetone solution of 1.6 g of a sodium salt of 2-ethylhexanoic acid, and the deposited crystals were collected by filtration, and dried to obtain 2.1 g of a sodium salt of D(−)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)propionic acid having a melting point of 115—8°C (decomp), yield 78.5%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1700, 1680, 1600 (—CON<, —$COO^{\ominus}$)

(2) In the same manner as in Example 32, 7 - [D(−) - α - (4 - methyl-2,3 - dioxo - 1 - piperazinocarbonylamino)propionamido] - 3 - acetoxymethyl - Δ^3-cephem - 4 - carboxylic acid was obtained from a sodium salt of D(−) - α - (4-methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)propionic acid and 7 - amino - 3-acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid. The thus obtained product was dissolved in 20 ml of acetone, and a solution of 0.65 g of a sodium salt of 2-ethylhexanoic acid in 5 ml of acetone was added to the resulting solution. The deposited crystals were collected by filtration and dried to obtain 1.2 g of sodium salt of 7 - [D(−) - α-(4 - methyl - 2,3 - dioxo - piperazinocarbonylamino)propionamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid having a melting point of 195°C (decomp.), yield 67.7%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1710—1660 (—CON<), 1600 (—$COO^{\ominus}$)

Example 36.

In the same manner as in Example 32, 7 - [D(−) - α - (4 - methyl - 2,3-dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - [5 - (1-methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid was obtained from 7 - amino - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]-Δ^3 - cephem - 4 - carboxylic acid and D(−) - α - (4 - methyl - 2,3 - dioxo - 1-piperazinocarbonylamino) - p - hydroxyphenylacetic acid.

Melting point (decomp.), 147—9°C; yield, 62.0%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1765 (lactam), 1720—1660 (—CON<, —COOH)

Example 37.

In the same manner as in Example 29, 7 - [D(−) - α - (4 - methyl - 2,3-dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - azidomethyl - Δ^3 - cephem-4 - carboxylic acid was obtained from D(−) - α - (4 - methyl - 2,3 - dioxo - 1-piperazinocarbonylamino)phenylacetic acid and 7 - amino - 3 - azidomethyl - Δ^3-cephem - 4 - carboxylic acid.

Melting point (decomp.), 185—8°C; yield, 68.0%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1775 (lactam), 1720—1660 (—CON<, —COOH)
νN_3 2090

Example 38.

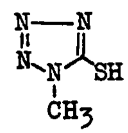
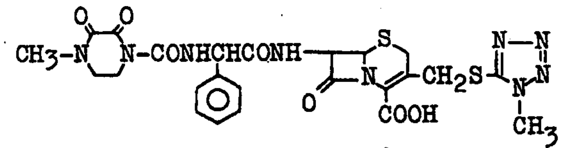
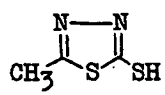
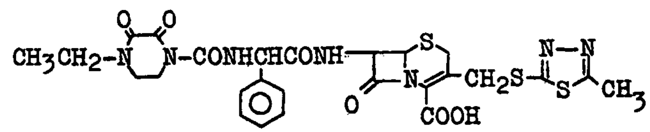
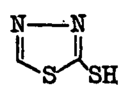
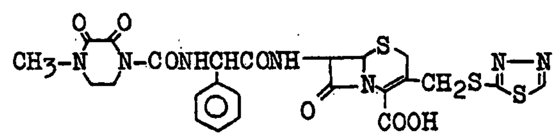
In 10 ml of a phosphoric acid buffer solution of a pH of 6.3 was suspended 0.57 g of 7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, and 0.07 g of sodium hydrogencarbonate was dissolved therein. To the solution was then added 0.12 g of 1-methyl-5-mercapto-1,2,3,4-tetrazole to dissolve the latter in the former, and the solution was subjected to reaction for 24 hours while maintaining the pH of the solution at 6.5—6.7 by using dilute hydrochloric acid and sodium hydrogencarbonate. After the reaction, the reaction liquid was cooled, and then adjusted to a pH of 5.0 by adding dilute hydrochloric acid. The reaction liquid was sufficiently washed with ethyl acetate, after which the aqueous layer was separated off and then adjusted to a pH of 1.5 by adding dilute hydrochloric acid thereto. The deposited crystals were collected by filtration and dried, after which the dried crystals were washed with ethyl acetate to obtain 0.40 g of 7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-

phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3-cephem - 4 - carboxylic acid, m.p. 163—165°C (decomp.), yield 74.5%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1775 (lactam), 1720—1660 (—CON<, —COOH)
NMR (d_6-DMSO) τ values: 0.18 (1H, d), 0.55 (1H, d), 2.64 (5H, s), 4.3 (1H, q), 4.4 (1H, d), 5.0 (1H, d), 5.75 (2H, s), 6.05 (5H, s), 6.3—6.8 (6H), 8.92 (3H, t)

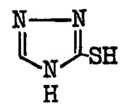
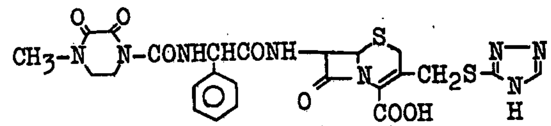
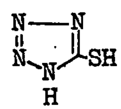
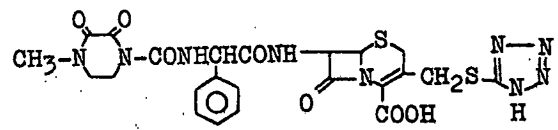
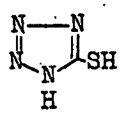
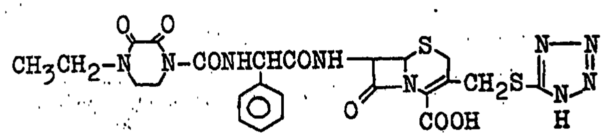
In the same manner as above, the objective compounds shown in Table 29 were obtained from 7 - [D(–) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonyl)-phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid or 7-[D(–) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]-3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid and the compounds of formula (VII) shown in Table 29. All the objective compounds were D(–) isomers, and the structure of each objective compound was confirmed by IR and NMR.

Table 29

Compound of formula (VII)	Objective compound
	 m.p. (decomp.) 168 - 170°C, yield 83 %
	 m.p. (decomp.) 150°C, yield 73.4 %
	 m.p. (decomp.) 158 - 159°C, yield 78.5 %

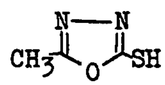
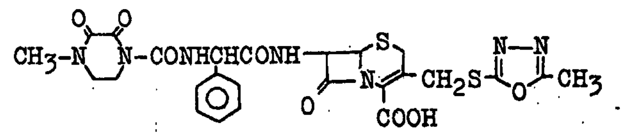
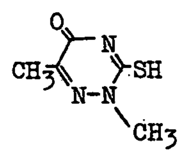
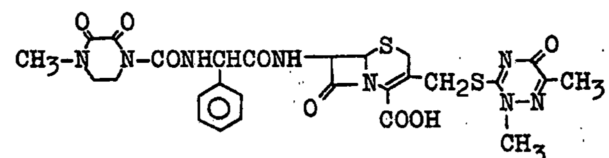
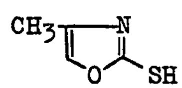
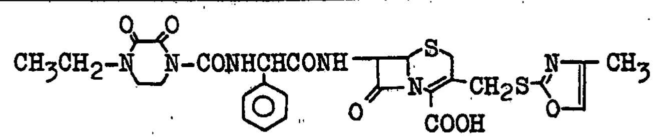
- cont'd -

Table 29 (Cont'd)

	 m.p. (decomp.) 175 - 180°C, yield 73.4 %
	 m.p. (decomp.) 163 - 165°C, yield 72.5 %
	 m.p. (decomp.) 159 - 160°C, yield 66 %

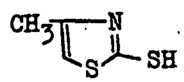
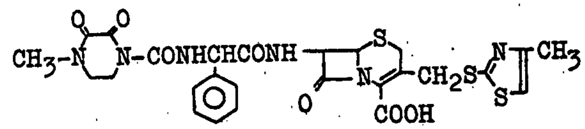
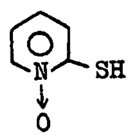
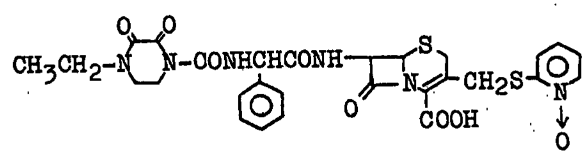
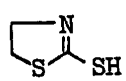
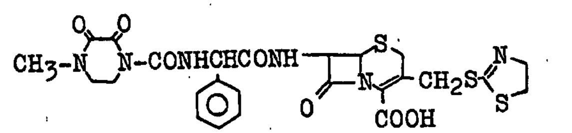
- cont'd -

Table 29 (Cont'd)

	 m.p. (decomp.) 128 - 129°C, yield 67.7 %
	 m.p. (decomp.) 95 - 98°C, yield 66.6 %
	 m.p. (decomp.) 175 - 180°C, yield 78.0 %

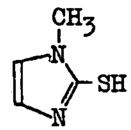
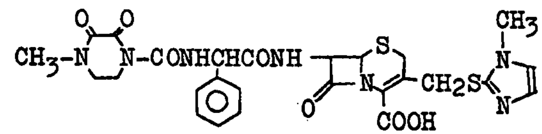
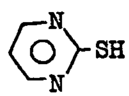
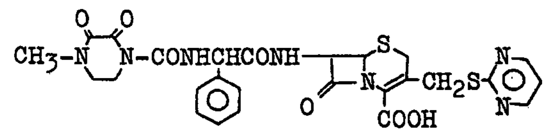
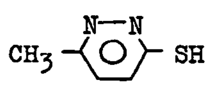
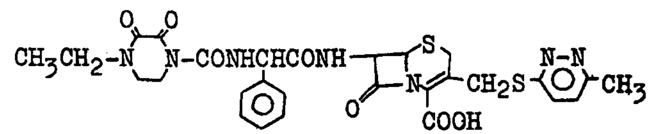
- cont'd -

Table 29 (Cont'd)

	 m.p. (decomp.) 156 - 157°C, yield 67.0 %
	 m.p. (decomp.) 177 - 180°C, yield 70.3 %
	 m.p. (decomp.) 180 - 182°C, yield 68.7 %

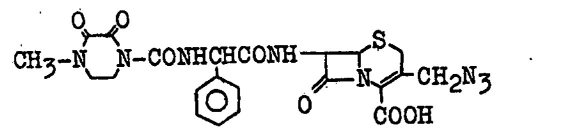
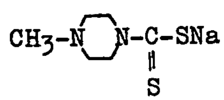
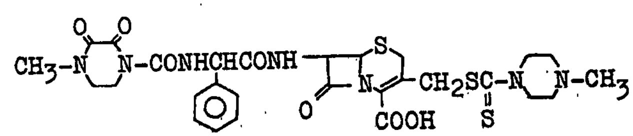
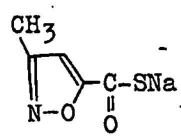
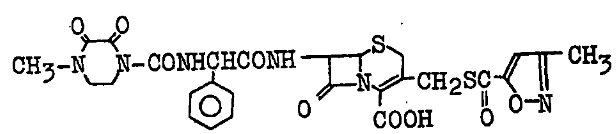
- cont'd -

Table 29 (Cont'd)

	 m.p. (decomp.) 182 - 184°C, yield 68 %
	 m.p. (decomp.) 192 - 194°C, yield 72.3 %
	 m.p. (decomp.) 175 - 178°C, yield 63.0 %

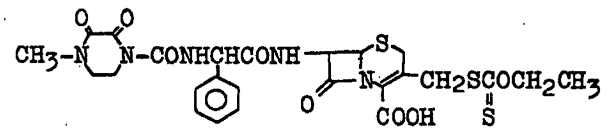
- cont'd -

Table 29 (Cont'd)

NaN_3	 m.p. (decomp.) 185 - 188°C, yield 78 %
	 m.p. (decomp.) 189°C, yield 64.6 %
	 m.p. (decomp.) 183°C, yield 69.1 %

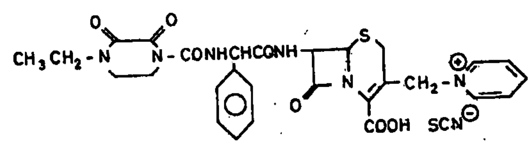
- cont'd -

Table 29 (Cont'd)

$CH_3CH_2OC(=S)-SNa$	 m.p. (decomp.) 181 - 183°C, yield 64.3 %

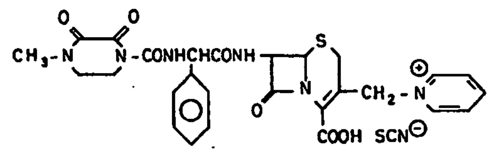
Example 39.

In 10 ml of water was suspended 1.15 g of 7 - [D(−) - α - (4 - ethyl - 2,3- dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ³- cephem - 4 - carboxylic acid, and 0.17 g of sodium hydrogencarbonate was then dissolved therein, after which 0.48 g of pyridine and 4.1 g of potassium thiocyanate were added thereto. The resulting mixture was subjected to reaction at 60°C for 5 hours while maintaining the pH of the mixture at 6.0 to 6.5 by adding dilute hydrochloric acid or sodium hydrogencarbonate. After the reaction, 20 ml of water was added to dilute the reaction mixture, which was then sufficiently washed with chloroform. The aqueous layer was then separated off and then adjusted to a pH of 1.5 by adding dilute hydrochloric acid. The deposited crystals were collected by filtration, dried, and then washed with acetone to obtain 1.04 g (yield, 79.6%) of a thiocyanic acid salt of 7- [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]- 3 - pyridinomethyl - Δ³ - cephem - 4 - carboxylic acid betaine having a melting point (decomp.) of 155—160°C, said product having the formula,



IR (KBr) cm^{-1}: $\nu_{C=O}$ 1780 (lactam), 1720—1660 (—CON<)
νSCN 2040

In the same manner as above, a thiocyanic acid salt of 7 - [D(–) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - pyridinomethyl - Δ^3 - cephem - 4 - carboxylic acid betaine was obtained from 7 - [D(–) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid and pyridine, said product having the formula,



Melting point (decomp.), 180—185°C; yield, 82.0%.

In a conventional manner, the above two products were treated with an ion exchange resin to obtain the desired 7 - [D(–) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - pyridinomethyl - Δ^3 - cephem - 4 - carboxylic acid betaine and 7 - [D(–) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - pyridinomethyl - Δ^3 - cephem - 4 - carboxylic acid betaine.

Example 40.

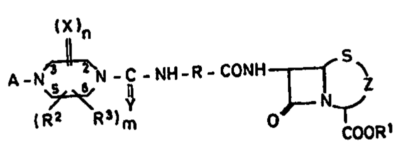
In 85 ml of anhydrous methanol was dissolved 1.5 g of a sodium salt of 7- [D(–) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (pyridyl - 1 - oxide)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid. To the resulting solution was added 0.65 g of anhydrous cupric chloride, and the resulting mixture was stirred at room temperature for 15 minutes and then subjected to reaction at 50°C for 14 hours. After the reaction, hydrogen sulfide gas was passed through the reaction solution with ice-cooling for 20 minutes. The resulting insolubles were filtered off, and the filtrate was concentrated under reduced pressure. To the residue was added 20 ml of a 5% aqueous sodium hydrogencarbonate solution, and the insolubles were filtered off, after which dilute hydrochloric acid was added to the filtrate to adjust the pH to 6.5. The filtrate was then washed with 10-ml portions of ethyl acetate three times, after which the aqueous layer was separated off and then adjusted to a pH of 1.8 by adding dilute hydrochloric acid thereto. The thus deposited crystals were collected by filtration and then dried under reduced pressure and washed with 20 ml of an ethyl acetate-chloroform mixed solvent (1:1 by volume) to obtain 0.40 g of 7- [D(–) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, m.p. 162—6°C (decomp.), yield 30.5%.

IR (KBr) cm^{-1}: $\nu_{C=O}$ 1770 (lactam), 1700 (—COOH), 1666 (—CON<)
NMR (d_6-DMSO) τ values: 0.13 (1H, d), 0.53 (1H, d), 2.61 (5H, s), 4.31 (1H, q), 4.41 (1H, d), 4.96 (1H, d), 5.82 (2H, s), 6.10 (2H, bs), 6.33 (2H, 2H, 2H, bs), 6.79 (3H, s), 8.89 (3H, t)

The word 'Nujol' used herein is a Registered Trade Mark.

WHAT WE CLAIM IS:—

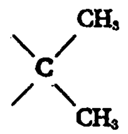
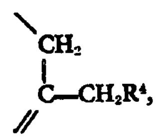
1. A compound represented by the general formula (I),



(I)

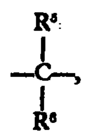
wherein R represents an amino acid residue; R^1 represents a hydrogen atom, an ester-forming group capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions, an ester-forming group capable of being easily removed by mammalian enzymic action, a silicon-phosphorus- or tin-containing group which is capable of being easily removed by treatment with H_2O or an alcohol, or a conven-

tional salt-forming cation; n represents 1 or 2; nX's, which may be the same or different, represent individually an oxygen or sulfur atom, and are linked in any combination at the 2-, 3- and 5- positions of the piperazine ring; m represents 4-n; each pair of R^2 and R^3 in linked to the same carbon atom, and m pairs of R^2 and R^3, which may be the same or different, represent individually a hydrogen atom, a halogen atom, a carboxyl group or an unsubstituted or substituted alkyl, cycloalkyl, aryl, acyl, aralkyl, alkoxycarbonylalkyl, acyloxyalkyl, alkoxy, alkoxycarbonyl, cycloalkyloxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, amino or carbamoyl group, any pair of R^2 and R^3 together with a common carbon atom may form a cycloalkyl ring; A represents a hydrogen atom, a hydroxy group, a nitro group, a cyano group, or an unsubstituted or substituted alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloalkenyl, cycloalkadienyl, aryl, acyl, aralkyl, acyloxyalkyl, alkoxy, cycloalkyloxy, aryloxy, alkoxycarbonyl, cycloalkyloxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, carbamoyl, thiocarbamoyl, acylcarbamoyl, acylthiocarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkylsulfonylthiocarbamoyl, arylsulfonylthiocarbamoyl, sulfamoyl, alkoxycarbonylthioalkyl, alkoxythiocarbonylthioalkyl, amino or heterocyclic group; Y represents an oxygen or sulfur atom, and

 represents  or 

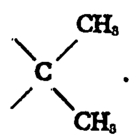
where R^4 represents a hydrogen atom, a hydroxy group, a cyano group, an azido group, a quaternary ammonium group, or an unsubstituted or substituted alkoxy, aryloxy, aralkoxy, acyloxy, carbamoyloxy, guanidino, amino, alkylthio, arylthio, aralkylthio, acylthio, thiocarbamoylthio, alkoxythiocarbonylthio, aryloxythiocarbonylthio, cycloalkyloxythiocarbonylthio, amidinothio or heterocyclylthio group.

2. A compound according to claim 1, wherein R is a group represented by the formula,

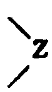
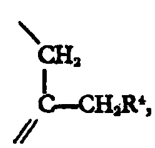


wherein R^5 represents a substituted or unsubstituted alkyl, cycloalkyl, cycloalkenyl, cycloalkadienyl, aryl, aralkyl, aryloxy, alkylthioalkyl, or heterocyclic group; and R^6 represents a hydrogen atom; or R^5 and R^6 together with a common carbon atom may form a cycloalkyl, cycloalkenyl or cycloalkadienyl ring.

3. A compound according to any one of claims 1 and 2, wherein

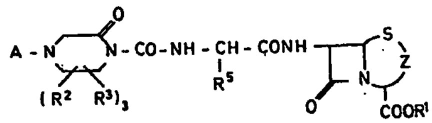
 is .

4. A compound according to any one of claims 1 and 2, wherein

 is 

where R^4 is as defined in claim 1.

5. A compound represented by the general formula (Ia),

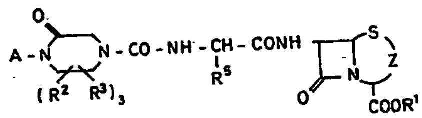


(Ia)

wherein R^1, R^2, R^3, A and

are as defined in Claim 1 and R^5 is as defined in Claim 2.

6. A compound represented by the general formula (Ib),

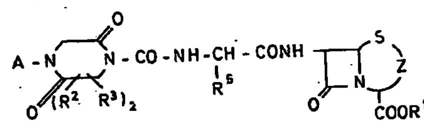


(Ib)

wherein R^1, R^2, R^3, A and

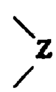
are as defined in Claim 1 and R^5 is as defined in Claim 2.

7. A compound represented by the general formula (Ic),



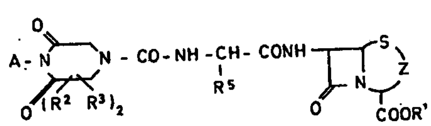
(Ic)

wherein R^1, R^2, R^3, A and



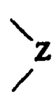
are as defined in Claim 1 and R^5 is as defined in Claim 2.

8. A compound represented by the general formula (Id),



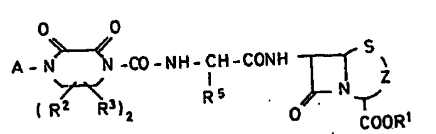
(Id)

wherein R^1, R^2, R^3, A and



are as defined in Claim 1 and R^5 is as defined in Claim 2.

9. A compound represented by the general formula (Ie),



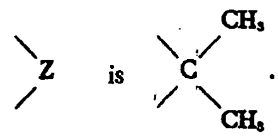
(Ie)

wherein R^1, R^2, R^3, A and

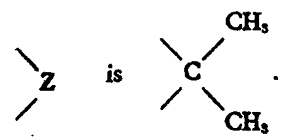
are as defined in Claim 1 and R^5 is as defined in Claim 2.

10. A compound according to Claim 9, wherein A is a hydrogen atom, or a substituted or unsubstituted alkyl, alkenyl, aryl or aralkyl group; and R^2 and R^3 are individually a hydrogen atom or an alkyl group.

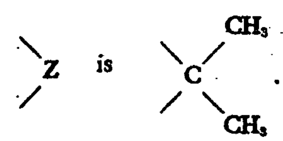
11. A compound according to Claim 5, wherein



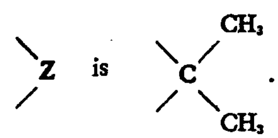
12. A compound according to Claim 6, wherein



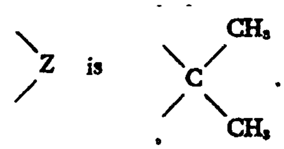
13. A compound according to Claim 7, wherein



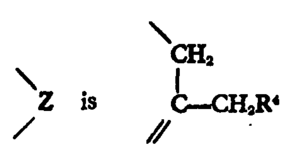
14. A compound according to Claim 8, wherein



15. A compound according to Claim 9, wherein



16. A compound according to Claim 9, wherein



in which R^4 is as defined above.

17. A compound according to Claim 1, wherein R^1 is a hydrogen atom.

18. A compound according to Claim 1, wherein R^1 is selected from ester-forming groups capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions and ester-forming groups capable of being easily removed owing to enzymes in a living body.

19. A compound selected from

6 - [D(-) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - dichloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - enanthoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - cyclohexanecarbonyl - 2 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - acetyl - 3 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - n - hexyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - n - butyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - n - butyl - 6 - methyl - 2 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - n - octyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - pivaloyloxymethyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - palmitoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - capryloyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - caproyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - chloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - benzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - p - chlorobenzoyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - p - methoxybenzoyl - 2 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - {D(-) - α - [4 - (3,4,5 - trimethoxybenzoyl) - 2 - oxo - 1 - piperazino-carbonylamino]phenylacetamido}penicillanic acid,

6 - {D(-) - α - [4 - (2,4 - dichlorobenzoyl) - 2 - oxo - 1 - piperazinocarbonyl-amino]phenylacetamido}penicillanic acid,

6 - [D(-) - α - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - phenylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid, and

6 - [D(-) - α - (4 - ethoxycarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid.

20. A compound selected from

6 - [D(-) - α - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - n - butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - isopropyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - n - pentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (4 - iso - pentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(-) - α - (2 - methyl - 4 - n - butyl - 3 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - n - butyl - 5 - methyl - 3 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(-) - α - (4 - n - butyl - 6 - methyl - 3 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - benzyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - β - hydroxyethyl - 3 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - acetyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - carbamoyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (2,5 - dimethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (5 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (2 - ethoxycarbonylmethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)propionamido]penicillanic acid,

6 - [D(−) - α - (4 - allyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - α - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - β - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - {D(−) - α - [4 - (trans - 2 - butenyl) - 3 - oxo - 1 - piperazinocarbonylamino]phenylacetamido}penicillanic acid,

6 - [D(−) - α - (4 - n - hexyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid.

6 - [D(−) - α - (4 - n - heptyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - octyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - dodecyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - cyclopentyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - phenylaminocarbonyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (2 - phenyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid, and

6 - [D(−) - α - (4 - morpholinomethyl - 3 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid.

21. A compound selected from

6 - [D(−) - α - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - benzoyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - methyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid, and

6 - [D(−) - α - (4 - benzyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid.

22. A compound selected from

6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - acetoxyethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - allyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(−) - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido]penicillanic acid,

6 - [D(−) - α - (4 - β - chloroethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (6 - methyl - 4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4,6 - dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)-phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-cyclohexadienylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-cyclohexadienylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-1,4 - cyclohexadienylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-cyclohexadienylacetamido]penicillanic acid,

6 - [DL - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2-thienylacetamido]penicillanic acid,

6 - [DL - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienyl-acetamido]penicillanic acid,

6 - [DL - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperadinocarbonylamino) - 2-thienylacetamido]penicillanic acid, and

6 - [DL - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2-thienylacetamido]penicillanic acid.

23. A compound selected from

6 - [D(−) - α - (2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]-penicillanic acid,

6 - [D(−) - α - (2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piperazinocarbonyl-amino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - benzyl - 2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanic acid,

6 - [D(−) - α - (4 - β,β,β - trichloroethoxycarbonyl - 2,2 - pentamethylene-3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid, and

6 - [D(−) - α - (4 - benzyl - 2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piper-azinocarbonylamino)phenylacetamido]penicillanic acid.

24. A compound selected from

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-

phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α -(4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)-phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)-phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3-cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3-cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 6 - methyl - 2,3 - dioxo - 1 - piperazinocarbonyl-amino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]-Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4,6 - dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3-cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)pro-pionamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-

hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - azidomethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - oxadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [3 - (2,6 - dimethyl - 5 - oxo - 2,5 - dihydro - 1,2,4 - triazinyl)-thiomethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (4 - methyloxazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (4 - methylthiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (pyridyl - 1 - oxide) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - (2 - thiazolinylthiomethyl) - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1 - methylimidazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - (2 - pyrimidinylthiomethyl) - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [3 - (6 - methylpyridazinyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [1 - (4 - methylpiperazino) - thiocarbonylthiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (3 - methylisoxazolyl) - carbonylthiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - ethoxythiocarbonylthiomethyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - pyridinomethyl - Δ^3 - cephem - 4 - carboxylic acid betaine, and

7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - pyridinomethyl - Δ^3 - cephem - 4 - carboxylic acid betaine.

25. A compound selected from

7 - [D(−) - α - (4 - ethoxycarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - n - hexyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4- thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-

phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3-cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl]-Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]-3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,

7 - [D(−) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3-cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl- 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]-Δ^3 - cephem - 4 - carboxylic acid,

7 - [D(−) - α - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl-1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,

7 - [D(−) - α - (3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]-3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, and

7 - [D(−) - α - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid.

26. A compound selected from

pivaloyloxymethyl 6 - [D(−) - α - (2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,

phthalidyl 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,

phthalidyl 6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,

phthalidyl 6 - [D(−) - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,

phthalidyl 6 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,

methoxymethyl 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,

methoxymethyl 6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanate,

methoxymethyl 6 - [D(−) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido)penicillanate,

methoxymethyl 6 - [D(−) - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanate,

methoxymethyl 6 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanate,

pivaloyloxymethyl 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanate,

pivaloyloxymethyl 6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanate,

pivaloyloxymethyl 6 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanate,

β - piperidinoethyl 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanate,

β - piperidinoethyl 6 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanate,

β - morpholinoethyl 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanate,

β - morpholinoethyl 6 - [D(−) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanate, and

methoxymethyl 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylate.

27. A compound according to Claim 1, 5, 6, 7, 8 or 9, wherein R^1 is a cation capable of forming a non-toxic salt.

28. A non-toxic salt of a compound according to Claim 19, 20, 21, 22, 23, 24 or 25.

29. 6 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicillanic acid or its non-toxic salt.

30. 6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicillanic acid or its non-toxic salt.

31. 6 - [D(−) - α - (6 - methyl - 4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanic acid or its non-toxic salt.

32. 6 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] penicillanic acid or its non-toxic salt.

33. 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid or its non-toxic salt.

34. 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3-cephem - 4 - carboxylic acid or its non-toxic salt.

35. 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3-cephem - 4 - carboxylic acid or its non-toxic salt.

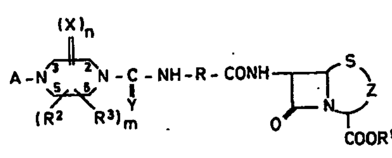
36. 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid or its non-toxic salt.

37. 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid or its non-toxic salt.

38. 7 - [D(−) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-p - hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid or its non-toxic salt.

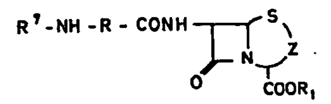
39. 7 - [D(−) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3-cephem - 4 - carboxylic acid or its non-toxic salt.

40. A process for producing a compound represented by the general formula (I),



(I)

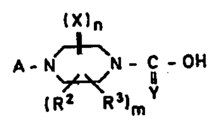
wherein R, A, X, n, m, R_1, R_2, R_3, Y and Z are as herein defined which comprises reacting a compound represented by the general formula (II),



(II)

wherein R' represents a hydrogen atom, a silicon or phosphorous containing group, which is capable of easy removal by treatment with water or an alcohol; R, R^1 and

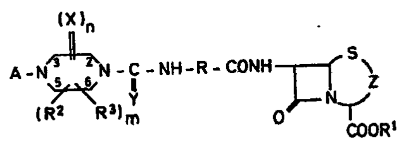
are as defined above, with a reactive derivative in the (thio)carboxyl group of a compound represented by the general formula (III),



(III)

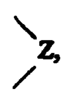
wherein A, X, Y, R^2, R^3, n and m are as defined above.

41. A process for producing a compound represented by the general formula (I),

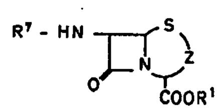


(I)

wherein A, Y, R, R^1, R^2, R^3, X,

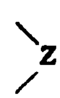


n and m are as defined in Claim 40, which comprises reacting a compound represented by the general formula (IV),

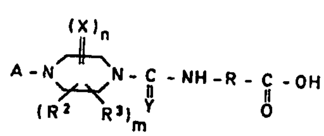


(IV)

wherein R^1, R' and



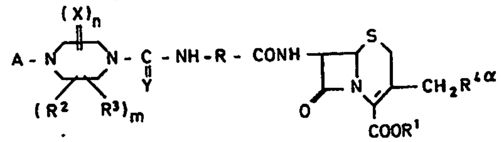
are as defined in Claim 40, with a compound represented by the general formula (V),



(V)

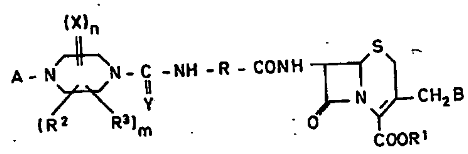
wherein A, R, R^2, R^3, X, Y, n and m are as defined in Claim 40, or with a reactive derivative in the carboxyl group of the compound of formula (V).

42. A process for producing a compound represented by the general formula (I'),



(I')

wherein A, R, R^1, R^2, R^3, X, Y, n and m are as defined in Claim 1 and R^{4a} represents a cyano group, an azido group, a quaternary ammonium group, or a substituted or unsubstituted alkoxy, aryloxy, aralkoxy, acyloxy, carbamoyloxy, guanidino, amino, alkylthio, arylthio, aralkylthio, acylthio, thiocarbamoylthio, alkoxythiocarbonylthio, aryloxythiocarbonylthio, cycloalkyloxythiocarbonylthio, amidinothio, or heterocyclylthio group, which comprises reacting a compound represented by the general formula (VI),



(VI)

wherein B represents a substituent capable of being easily replaced by a nucleophilic reagent; and A, R, R^1, R^2, R^3, X, Y, n and m are as defined in Claim 40, with a compound represented by the general formula (VII),

$$R^8M \qquad \text{(VII)}$$

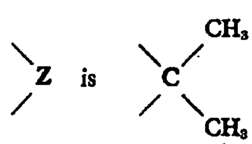
wherein M represents a hydrogen atom, or an alkali metal or alkaline earth metal atom; and R^8 represents a cyano group, an azido group or an organic group linked through O, N or S, or with a tertiary amine.

43. A process according to Claim 40, 41 or 42, wherein R is a group represented by the formula,

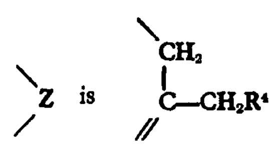
$$-\overset{R^5}{\underset{R^6}{C}}-,$$

in which R^5 is as defined in claim 2.

44. A process according to Claim 40 or 41, wherein



45. A process according to Claim 40 or 41, wherein



in which R^4 is as defined in Claim 40.

46. A process according to Claim 40 or 41, wherein R is

$$-\underset{R^5}{CH}-$$

in which R^5 is as defined in Claim 43, n is 1, m is 3, and X is an oxygen atom linked to the carbon atom at the 2-position of the piperazine ring.

47. A process according to Claim 40 or 41, wherein R is

$$-\underset{\substack{| \\ R^5}}{CH}-$$

in which R^5 is as defined in Claim 43, n is 1, m is 3 and X is an oxygen atom linked to the carbon atom at the 3-position of the piperazine ring.

48. A process according to Claim 40 or 41, wherein R is

$$-\underset{\substack{| \\ R^5}}{CH}-$$

in which R^5 is as defined in Claim 43, n is 2, m is 2 and the two X's are oxygen atoms linked to the carbon atoms at the 2- and 5-positions of the piperazine ring.

49. A process according to Claim 40 or 41, wherein R is

$$-\underset{\substack{| \\ R^5}}{CH}-$$

in which R^5 is as defined in Claim 43, n is 2, m is 2 and the two X's are oxygen atoms linked to the carbon atoms at the 3- and 5-positions of the piperazine ring.

50. A process according to Claim 40 or 41, wherein R is

$$-\underset{\substack{| \\ R^5}}{CH}-$$

in which R^5 is as defined in Claim 43, n is 2, m is 2 and the two X's are oxygen atoms linked to the carbon atoms at the 2- and 3-positions of the piperazine ring.

51. A process according to Claim 42 or 45, wherein R is

$$-\underset{\substack{| \\ R^5}}{CH}-$$

in which R^5 is as defined in Claim 43; n is 2; m is 2; and the two X's are oxygen atoms linked to the carbon atoms at the 2- and 3-positions of the piperazine ring.

52. A process according to Claim 46, wherein

$$>Z \text{ is } >C\begin{matrix} CH_3 \\ CH_3 \end{matrix}.$$

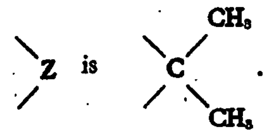
53. A process according to Claim 47, wherein

$$>Z \text{ is } >C\begin{matrix} CH_3 \\ CH_3 \end{matrix}.$$

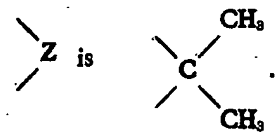
54. A process according to Claim 48, wherein

$$>Z \text{ is } >C\begin{matrix} CH_3 \\ CH_3 \end{matrix}.$$

55. A process according to Claim 49, wherein

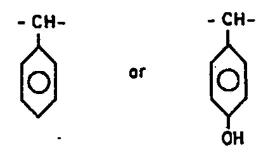


56. A process according to Claim 50, wherein

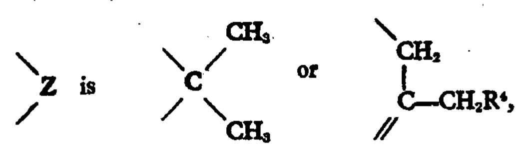


57. A process according to Claim 40, 41 or 42, wherein A is a hydrogen atom, or a substituted or unsubstituted alkyl, alkenyl, aryl or aralkyl group; and R^2 and R^3 are individually a hydrogen atom or an alkyl group.

58. A process according to Claim 40 or 41, wherein R is

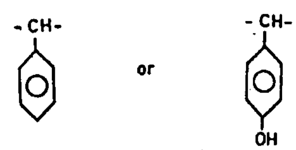


n is 2; m is 2 and two X's are oxygen atoms linked to the carbon atoms at the 2- and 3-positions of the piperazine ring, each pair of R^2 and R^3, which may be the same or different, are individually a hydrogen atom or a methyl group, A is a methyl or ethyl group, R^1 is a hydrogen atom or a cation capable of forming a non-toxic salt and



in which R^4 is an acetoxy, 5 - (2 - methyl - 1,3,4 - thiadiazolyl) - thio, 5 - (1,3,4-thiadiazolyl) - thio, 2 - (1 - methyl - 1,3,4 - triazolyl) - thio, 5 - (1 - methyl - 1,2,3,4-tetrazolyl) - thio or 5 - (1,2,3,4 - tetrazolyl) - thio group.

59. A process according to Claim 42, wherein R is



n is 2, m is 2; two X's are oxygen atoms linked to the carbon atoms at the 2- and 3-positions of the piperazine ring; each pair of R^2 and R^3, which may be the same or different, are individually a hydrogen atom or methyl group; A is a methyl or ethyl group; and R^1 is a hydrogen atom or a cation capable of forming a non-toxic salt.

60. A process according to Claim 42, wherein R^4 and R^8 are the same and selected from, 5 - (2 -methyl - 1,3,4 - thiadiazolyl) - thio, 5 - (1,3,4 - thiadiazolyl) - thio, 5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thio, and 5 - (1,2,3,4 - tetrazolyl) - thio groups.

61. A process according to Claim 40 or 41, wherein R^7 is a hydrogen atom.

62. A process according to Claim 40, 41 or 42, wherein R^1 is a cation capable of forming a salt.

63. A process according to Claim 62, wherein the salt is a non-toxic salt.

64. A process according to Claim 40, 41 or 42 wherein R^1 is selected from the

group consisting of ester-forming groups capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions and ester-forming groups capable of being easily removed owing to enzymes in a living body.

65. A process according to Claim 40 or 41, wherein R^1 is a trialkylammonium.

66. A process according to Claim 40, wherein the reactive derivative in the (thio)-carboxyl group of a compound of formula (III) is an acid halide.

67. A process according to Claim 41, wherein the reactive derivative in the carboxyl group of a compound of formula (V) is a mixed acid anhydride.

68. A process according to Claim 40 or 41, wherein the reaction is carried out in the presence of an acid-binding agent.

69. A process according to Claim 41, wherein the reaction is carried out in the presence of a dehydrating condensing agent.

70. A process according to Claim 40 or 41, wherein at least one of R^1 and R^7 is a silicon, or a phosphorus containing group capable of easy removal by treatment with water or an alcohol.

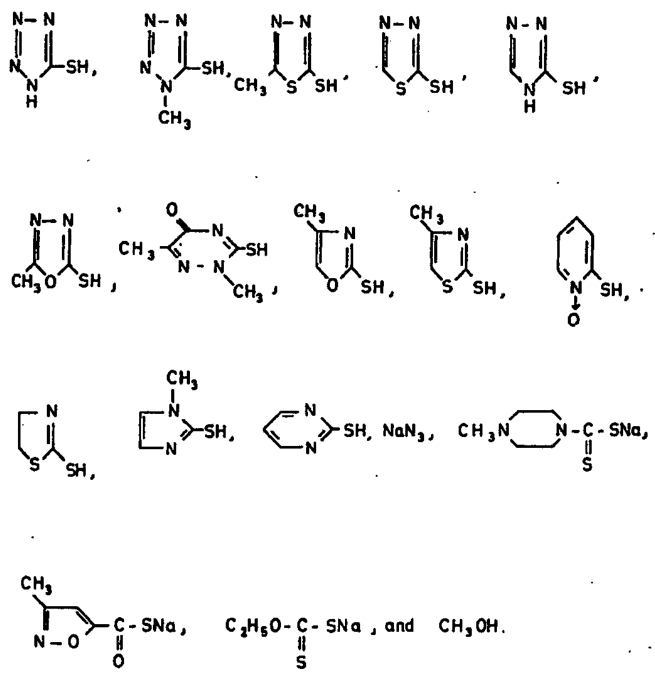
71. A process according to Claim 40 or 41, wherein the reaction is carried out at a temperature of $-60°$ to $+80°C$.

72. A process according to Claim 42, wherein B is a halo-substituted or unsubstituted lower alkanoyloxy group.

73. A process according to Claim 42, wherein B is an acetoxy group.

74. A process according to Claim 42, wherein R^8 is an organic group linked through O or S.

75. A process according to Claim 42, wherein the compound (VII) is selected from



76. A process according to Claim 42, wherein the tertiary amine is pyridine.

77. A process according to Claim 42, wherein the reaction is carried out in a polar solvent at a pH of 2 to 10.

78. A process according to Claim 42, wherein the reaction is carried out at a temperature of 0° to 100°C.

79. A process according to Claim 42, wherein B is a hetero aromatic amine N-oxide thio group having a thio group on the carbon atom adjacent to the N-oxide in the molecule, and the reaction is effected in the presence of a cupric compound.

80. A pharmaceutical composition containing as an active ingredient the compound as claimed in Claim 1.

For the Applicants:
F. J. CLEVELAND & COMPANY,
Chartered Patent Agents,
Lincoln's Inn Chambers,
40—43 Chancery Lane,
London, WC2A 1JQ.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1978.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.